



Final Report • February 12, 2014

SINGLE DOSE TOXICITY STUDY OF ER176 IN SPRAGUE DAWLEY RATS

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SRI Study Number: M038-13

SRI Project Number: P21877.100

Study Initiation: June 7, 2013

Experimental Work Performed:

Start: June 12, 2013
Finish: November 8, 2013

Study Completion: February 12, 2014

Sponsor:

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National Institute of Mental Health, NIH, DHHS
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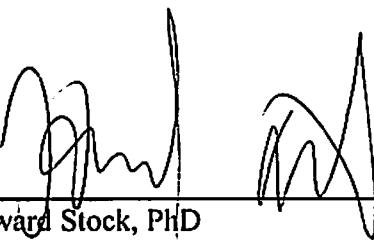
Sponsor's Representative: Jamie Driscoll, Project Officer, NIMH
Robert Innis, Ph.D. Investigator, NIMH

NIMH Contract and WA Number: HHS271200900018C, WA#16

**Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13**

APPROVAL SIGNATURES

Written by:



Howard Stock, PhD
Study Director

12 Feb 2014
Date

Approved by:



Hanna Ng, PhD, DABT
Director, Preclinical Safety

2/12/2014
Date

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SUMMARY

The objective of this study was to determine potential toxic effects and to identify potential target organs of toxicity, if possible, for the toxicity endpoints examined following a single intravenous (iv) bolus administration of ER176 given to Sprague Dawley rats. Additionally, the maximum tolerated dose (MTD) and no observed adverse effect level (NOAEL) of ER176 in rats may be established. Information from this study may be used to determine the suitability of the proposed human dose.

Two groups of 10 male and 10 female rats were administered a single dose of either the vehicle control (Group 1) or ER176 at 88.1 $\mu\text{g}/\text{kg}$ (528.6 $\mu\text{g}/\text{m}^2$; 100 times the human dose; Group 2) on Day 1 by iv bolus injection into the tail vein. The vehicle was 10% ethanol and 90% saline. In Groups 1 and 2 five males and five females in each group were sacrificed on Day 3, while the remaining animals were sacrificed on Day 15. In-life evaluations of mortality, morbidity and clinical observations were conducted daily. Body weights were collected on Days 1, 3 and 15. Food consumption was evaluated twice weekly. Clinical pathology samples were collected on the day the animals were euthanized. All animals survived to their scheduled sacrifices. There were no test article-related effects seen in the animals treated with 88.1 $\mu\text{g}/\text{kg}$ ER176 on body weights, food consumption, clinical pathology, gross necropsy, organ weights or histopathology, compared with the controls. However, slight ataxia was observed immediately post dose administration in 10 of 10 males and 6 of 10 females in the ER176 treated group. The effect was slight and transient, and the animals recovered quickly (within 2 hr post dose administration). All animals in the control group were normal. Due to this clinical finding and in an attempt to establish the NOAEL, additional animals were evaluated for clinical observations after consultation with the Sponsor.

Three groups of 10 male and 10 female rats were administered ER176, by iv tail vein injection, at 22.0 $\mu\text{g}/\text{kg}$ (132.5 $\mu\text{g}/\text{m}^2$; 25 times the human dose; Group 3), 44.1 $\mu\text{g}/\text{kg}$ (264.3 $\mu\text{g}/\text{m}^2$; 50 times the human dose; Group 4), or 88.1 $\mu\text{g}/\text{kg}$ (528.6 $\mu\text{g}/\text{m}^2$; 100 times the human dose; Group 5). In-life evaluations of mortality, morbidity and clinical observations were conducted daily for 3 days, and animals were sacrificed on Day 3. No test article-related effects were observed in the animals treated with 22.0 or 88.1 $\mu\text{g}/\text{kg}$ of ER176 (Groups 3 and 5). However, a slight and transient ataxia was observed in one male rat immediately following dosing in the 44.1 $\mu\text{g}/\text{kg}$ dose group (Group 4). It is not clear why animals in the high dose groups (100 times the human dose; 88.1 $\mu\text{g}/\text{kg}$) responded differently to ER176 in Groups 2 and 5 in clinical observations immediately post dose administration. It may be due to animal-to-animal variations in different shipments.

In conclusion, a single dose of ER176 (22.0 $\mu\text{g}/\text{kg}$, 132.5 $\mu\text{g}/\text{m}^2$; 25 times the projected human dose) administered intravenously was well tolerated in rats and produced no significant treatment-related effects. Animals in the 44.1 and 88.1 $\mu\text{g}/\text{kg}$ treatment groups also tolerated the single dose administration, except a slight and transient ataxia was observed. The NOAEL is considered to be 22.0 $\mu\text{g}/\text{kg}$ (132.5 $\mu\text{g}/\text{m}^2$; 25 times the projected human dose). The MTD is considered to be greater than 88.1 $\mu\text{g}/\text{kg}$ (528.6 $\mu\text{g}/\text{m}^2$; 100 times the projected human dose).

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QUALITY ASSURANCE UNIT

**Final Report and
Conflict of Interest Statement**

SRI's Quality Assurance Unit assures that the study-- *Single Dose Toxicity Study of ER176 in Sprague Dawley Rats, SRI Study Number M038-13*-- has been reviewed for adherence to U.S. Food and Drug Administration Good Laboratory Practice Regulations (21 CFR Part 58).

The following inspections were conducted during this study:

<u>Phase Inspected</u>	<u>Date of Inspection</u>	<u>Date Findings Reported to Management/Study Director</u>
Protocol	05-22-13	05-22-13
Protocol, Attachment A	06-05-13	06-05-13
Protocol Amendment No. 1	10-09-13	10-09-13
Protocol Amendment No. 2	11-21-13	11-21-13
Dose Verification / Homogeneity / Dose Prep	06-10-13	06-10-13
Randomization	06-11-13	06-11-13
Blood Collection / Necropsy	06-26-13	06-26-13
Dose Verification / Homogeneity / Dose Prep	10-21-13	10-21-13
Test System / Dosing / Weights / Clin. Obs.	10-22-13	10-22-13
Draft Final Report and Raw Data	01-16-14	01-23-14
Final Report Verification	02-12-14	02-12-14

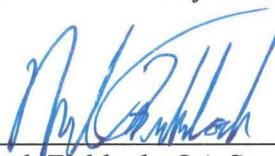
This statement certifies that the personnel listed below participated in the inspections and audit of this study. These personnel have not been involved in the generation or evaluation of the data. Participation by the individuals listed below poses no conflict of interest.

Noah Fishlock

Beverly Beatty

Esther Yau

Thomas Bregante



Noah Fishlock, QA Specialist
SRI Quality Assurance Unit

12 Feb 14

Date

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
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ORIGINAL



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QA STATEMENT

This study was audited by the VDx Quality Assurance Unit as required by U.S. Food and Drug Administration Good Laboratory Practice Regulations (21 CFR part 58). This QA Statement covers *laboratory processing* for samples received.

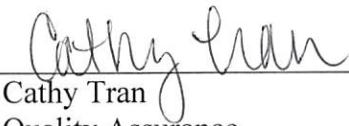
Client Name: SRI International / National Institutes of Health

Study ID: M038-13

VDx Accession #: RSR070113

The following inspections were performed:

Date of Inspection	Phase Inspected	Date Reported to VDx Management	Date Reported to the Study Director/designee
7/8/13 – 7/9/13	Trimming	7/11/13	7/11/13
7/16/13	Sectioning	7/30/13	7/30/13


Cathy Tran
Quality Assurance


Date

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KEY PERSONNEL

Name	Functional Role
Ken Altera, DVM, PhD, DACVP	Veterinary Pathologist, Westpath Corporation
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Naseem Chini, CLS (CA), MT (ASCP)	Director, Clinical Analysis Laboratory
Monica Doan, BS	Technical Monitor
Joan-Huey Dow, PhD	Manager, Analytical Chemistry
Ken López, DVM, MPH, DACLAM	Attending Veterinarian
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Linh Nguyen, BS	Supervisor, Dose Preparation
John Peauroi, DVM, MPVM, DACVP	Supervisor, Veterinary Diagnostics
Howard Stock, Ph.D	Study Director
Karen Tinajero, DVM	Clinical Veterinarian

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I. PURPOSE OF STUDY

The purpose of this study was to provide data of suitable quality and integrity to support applications to the U.S. Food and Drug Administration (FDA) and other regulatory agencies. Therefore, this study was performed in accordance with the U.S. FDA “Good Laboratory Practice for Nonclinical Laboratory Studies” (GLP) as described in 21 CFR Part 58.

II. STUDY OBJECTIVE

The objective of this study was to determine potential toxic effects and to identify potential target organs of toxicity, if possible, for the toxicity endpoints examined following a single intravenous (iv) bolus administration of ER176 given to Sprague Dawley rats. Additionally, the maximum tolerated dose (MTD) and no observed adverse effect level (NOAEL) of ER176 in rats were established (see Section VI. Discussions and Conclusion). Information from this study may be used to determine the suitability of the proposed human dose.

The protocol and amendments are presented in Appendix A.

III. EXPERIMENTAL DESIGN

Group	Target Dose^{a,*}	µg/m²	µg/kg	Dose Con. (µg/ml)	Dose Volume (ml/kg)^a	# Rats Sacrificed	
						Day 3 Main^{**}	Day 15 Recovery
1	0 (vehicle)	0	0	0	5	5M/5F	5M/5F
2	ER176 100x Human Dose	528.6	88.1	17.6	5	5M/5F	5M/5F
3 ^b	ER176 25x Human Dose	132.5	22.0	4.4	5	10M/10F	N/A
4 ^c	ER176 50x Human Dose	264.3	44.1	8.8	5	10M/10F	N/A
5 [*]	ER176 100x Human Dose	528.6	88.1	17.6	5	10M/10F	N/A
	Total # of Rats					40 M/40 F	10 M/10 F

^a The dose volume was not adjusted to achieve the target dose levels based on actual measured concentration of dose solution.

* Maximum human dose of ER176 is 10 µg per 70 kg person. $10 \mu\text{g}/70 \text{ kg} = 0.143 \mu\text{g/kg} \times 37$ (human surface area conversion) = 5.286 µg/m². Scaling for the rat gives $5.286 \mu\text{g/m}^2 / 6$ (rat surface area conversion) = 0.881 µg/kg as an equivalent human dose. $100 \times 0.881 = 88.1 \mu\text{g/kg}$.

^b Maximum human dose of ER176 is 10 µg per 70 kg person. $10 \mu\text{g}/70 \text{ kg} = 0.143 \mu\text{g/kg} \times 37$ (human surface area conversion) = 5.286 µg/m². Scaling for the rat gives $5.286 \mu\text{g/m}^2 / 6$ (rat surface area conversion) = 0.881 µg/kg as an equivalent human dose. $25 \times 0.881 = 22.0 \mu\text{g/kg}$. Surface area conversion: $5.286 \mu\text{g/m}^2 \times 25 = 132.5 \mu\text{g/m}^2$

^c Maximum human dose of ER176 is 10 µg per 70 kg person. $10 \mu\text{g}/70 \text{ kg} = 0.143 \mu\text{g/kg} \times 37$ (human surface area conversion) = 5.286 µg/m². Scaling for the rat gives $5.286 \mu\text{g/m}^2 / 6$ (rat surface area conversion) = 0.881 µg/kg as an equivalent human dose. $50 \times 0.881 = 44.1 \mu\text{g/kg}$. Surface area conversion: $5.286 \mu\text{g/m}^2 \times 50 = 264.3 \mu\text{g/m}^2$

** Day 1 is the day of dose administration

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Species and Strain: Sprague Dawley rat

Route of Administration: Intravenous (iv) via tail vein

Frequency: Single dose on Day 1

Dosing Volume: 5 ml/kg; slow bolus. Dose volumes were calculated based on the animal's most recent body weight.

Duration of In-life Phase: 15 days

IV. MATERIALS AND METHODS

A. Test and Control Articles

1. Test Article: ER176

Supplier: PET Chemistry, MIB/NIMH/NIH (Bethesda, MD)

Manufacturer: Dipartimento Scienze Farmaceutiche (Universita di Pisa)

Lot Number: 040711-2

Physical Description: Yellow crystals

Storage Conditions: -25 to -10°C

Characterization of Test Article: Characterization of the test article is the responsibility of the Sponsor. A Certificate of Analysis (CofA) was provided to SRI for inclusion in the final report (see Appendix B-1). The raw data generated by the Sponsor in support of this CofA was not verified or maintained by SRI. Test article chromatographic purity was analyzed by SRI before and after the test article was used for study.

2. Vehicle Control: 10% Ethanol/90% Saline

Component #1: Ethyl Alcohol, 200 Proof, Absolute, Anhydrous, ACS/ USP

Supplier: Pharmco AAPER

Manufacturer: Pharmco Products Inc. (Brookfield, CT)

Lot Number: SK1984

Physical Description: Clear, colorless liquid

Storage Conditions: Room temperature, 20.0–25.5°C

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Component #2:	0.9% Sodium Chloride Injection, USP
Supplier:	VWR (Visalia, CA)
Manufacturer:	Baxter Healthcare Corporation (Deerfield, IL)
Lot Number:	C879213, C90154
Physical Description:	Clear, colorless liquid
Storage Conditions:	Room temperature, 20.0–26.5°C
Characterization of Vehicle Control:	Information on the identity, purity, and stability of the control article were obtained by recording all of the pertinent information provided on the container labels or in a CofA provided by the supplier.
3. Preparation of Dose Formulations:	<p>Dose formulations were prepared by mixing the appropriate amount of test article in the vehicle to achieve the target concentration, and using a sterile stir bar and/or sonication to mix the formulation. Details of dose formulation preparation are described as follows.</p> <p>Dose formulations were prepared under yellow light, using an aseptic technique.</p> <p>The vehicle for Group 1 was prepared by mixing appropriate volume of ethanol with appropriate volume of saline to make a 10% ethanol/90% saline (v/v) solution, and the solution was mixed using a sterile stir bar on a magnetic stirrer for 15 min.</p> <p>To prepare the ER176 formulations, first, a stock solution of 40 µg/ml of ER176 in 10% ethanol (v/v), 90% saline was prepared by dissolving the appropriate amount of test article in ethanol. The solution was mixed by swirling for 2 min, then saline was added, and the solution was mixed again by sterile stir bar on a magnetic stirrer for 15 min. The 17.6 µg/ml (for Groups 2 and 5), 8.8 µg/ml (for Group 4), and 4.4 µg/ml (for Group 3) dose formulations were prepared by serial dilutions from the 40 µg/ml stock solution and were mixed by a sterile stir bar on a magnetic stirrer for 10 min. The vehicle and ER176 dose formulations were sterile filtered through Pall Acrodisc® Syringe Filter 0.2µm Supor® EKV Membrane (Low Protein Binding, Non-Pyrogenic, Lot number 7935439,</p>

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Expiration Date: 2015-08) into sterile, amber serum glass bottles. The vehicle and ER176 dose formulations were observed to be clear, colorless solutions.

Storage of Dose Formulations:

Dose formulations were stored refrigerated at 3.0-4.0°C, protected from the light in amber serum glass vials, for up to 2 days, until the day of use. Formulations were brought to room temperature prior to administration to the animals.

4. Characterization of Dose Formulations:

Assays to verify dose formulation, concentration and homogeneity, and stability under the conditions of the study were performed by SRI prior to the study (see Appendix B-2). Verification of dose formulation concentration was performed before administration. All dose verification results met the protocol criterion, being within $100.0 \pm 10.0\%$ of nominal concentration.

Mock formulations at nominal concentrations of 4 to 40 µg/ml were tested to determine the formulation stability. The results indicated that formulations at a nominal concentration range of 4 to 40 µg/ml were stable for at least 3 days refrigerated (2.5 to 4.0°C) and 1 day at room temperature after refrigeration (20.0 to 23.5°C).

Chromatographic purity results supported that the test article was stable during the study period.

5. Test Article Handling:

At a minimum personnel handling the test and control article formulations wore eye protection, gloves, and a protective smock or laboratory coat.

6. Disposition:

At the end of the study any remaining partially used and unused containers of vehicle control and test article will be shipped to the Sponsor.

Residual dose formulations will be discarded after analysis, when the final report is submitted, or when samples no longer afford evaluation.

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Empty control and test article containers may be destroyed by SRI on submission of the final report to the Sponsor.

See Section IV.I for information about retention of records and study samples.

7. Method for Assuring Correct Dosing:

The administration of each dose formulation was properly documented, and the amount administered to each animal was recorded.

B. Test System

Species:	Rat
Strain:	Sprague Dawley
Supplier:	Charles River (Hollister, CA)
Number of Animals:	100 assigned to test
Sex:	50 males and 50 females
Age at First Dose:	7–9 weeks
Weight Range At First Dose:	261–290 g (males) 168–196 g (females)
Animal Care:	General procedures for animal care and housing were in accordance with the National Research Council (NRC) <i>Guide for the Care and Use of Laboratory Animals</i> , 8 th edition (2011) and the Animal Welfare Standards incorporated in 9 CFR Part 3, 1991.
Quarantine:	3 days
Housing:	2–3 per cage
Cages:	Hanging polycarbonate cages with hardwood chip bedding
Light Cycle:	12 hr light/12 hr dark
Temperature:	66–73°F
Humidity:	35–56%

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Ventilation:	At least 10 room volumes per hour, with no recirculation of air.
Food:	Harlan Teklad Certified Rodent Chow #2018C, <i>ad libitum</i> . Feed is analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed are not present at levels that would affect the study. Documentation of feed analyses is maintained at SRI for reference. A copy of the lot specific reports provided by the supplier will be maintained in the study records.
Water:	Water (purified, reverse osmosis) was provided <i>ad libitum</i> . Based on previous reports, no contaminants that could interfere with and affect the results of the study are expected to be present in the water. Copies of annual analysis reports are maintained at SRI for reference.

Assignment of Animals to Study

Day:	1 day before initiation of treatment.
Randomization:	Animals were randomly assigned to treatment groups via a computerized body weight stratification procedure (Provantis version 8.6.1.3).
Identification:	Animals were individually identified by a unique ear punch.
Welfare of the Animals:	Every effort was made to minimize, if not eliminate, pain and suffering in all animals in this study. The Study Director made every effort to protect the scientific validity of the study. There were no moribund animals on this study.

C. Experimental Procedure (In-Life Evaluations)

- 1. Dose Administration:** Intravenous (iv) injection. This route of administration is proposed for clinical use of the test article in humans.
- 2. Mortality/Morbidity:** Animals were checked at least once daily
- 3. Clinical Observations:** For Groups 1-2: Recorded immediately post dose and approximately 2–4 hr post dose on treatment days and once daily on Days 2–15, or more often as

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clinical signs warrant, and on the day of necropsy. Animals were examined for any altered clinical signs, including gross motor and behavioral activity, and observable changes in appearance.

For Groups 3–5: Recorded immediately post dose and approximately 15, 30, 60, 90, and 120 minutes post dose on treatment day; once on Day 2, or more often as clinical signs warrant; and on the day of necropsy.

4. Body Weights: Body weights were recorded on Day 1 (pre-dose) and Day 3 for all animals, and additionally on Day 15 for recovery animals.

5. Food Consumption: For Groups 1 and 2: Quantitatively measured for approximately a 24 hr period twice weekly for each cage throughout the study. The total cage consumption per interval was divided by the number of animals in the cage to determine the average daily food consumption per animal.

For Groups 3–5: Food consumption was not measured.

6. Clinical Pathology Evaluations:

Preparation of Animals: Animals were not fasted before blood collection.

Method of Collection: Blood was collected from the retro-orbital sinus of rats under 60% CO₂/40% O₂ anesthesia. Hematology samples were collected using K₃EDTA as the anticoagulant. No anticoagulant was used for serum chemistry samples.

Frequency: For Groups 1 and 2: On Day 3 for animals scheduled for main sacrifice and Day 15 for recovery animals.

For Groups 3–5: Clinical pathology was not measured.

Clinical pathology parameters that were evaluated are listed below. In some cases automated analyzers report additional parameters not specified in the protocol. Results for the additional parameters were included in the data package, but

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were not summarized, analyzed, or reported, and their collection was not considered a deviation from the protocol.

Hematology Parameters:

- Hematocrit (HCT)
- Hemoglobin (HGB)
- Red blood cell count (RBC)
- Red blood cell distribution width (RDW)
- White blood cell count (WBC)
- WBC differential and absolute counts
 - Total neutrophil (ANS)
 - Percentage neutrophil (PNS)
 - Total lymphocyte (ALY)
 - Percent lymphocyte (PLY)
 - Total monocyte (AMO)
 - Percent monocyte (PMO)
 - Total eosinophil (AEO)
 - Percent eosinophil (PEO)
 - Total basophil (ABA)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCC)
- Platelet count (PLC)
- Mean platelet volume (MPV)
- Reticulocyte count (absolute, REA, and percent, RET)

Serum Chemistry Parameters:

- Bilirubin, total (TBI)
- Creatinine (CRE)
- Sodium (SOD)
- Potassium (POT)
- Chloride (CHL)
- Cholesterol (CHO)
- Triglycerides (TRI)
- Glucose (GLU)
- Blood urea nitrogen (BUN)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (ALP)
- Calcium (CAL)
- Phosphorus (PHO)

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- Protein, total (TPR)
- Albumin (ALB)
- Albumin/globulin ratio (AGR)
- Globulin (GLO)

D. Necropsy

Interval:	For Groups 1 and 2: Day 3 (main) and Day 15 (recovery) for designated animals.
	For Groups 3–5: Day 3. Gross necropsies and histopathology were not performed.
Euthanasia:	An overdose of sodium pentobarbital administered by intraperitoneal injection.
Observations:	External examination of all body orifices and an examination of all cranial, thoracic, and abdominal organs were performed, and all gross findings were recorded.
Tissues Retained:	The following tissues were collected from all animals in the Main Group and the Recovery Group. Tissues were retained in 10% neutral buffered formalin, except where noted: <ul style="list-style-type: none">• All gross lesions (including tissue masses and abnormal regional lymph nodes)• Adrenal glands• Aorta• Bone (femur with femoro-tibial joint)• Bone, sternum (marrow histology)• Bone marrow smear, sternum (for cytology)• Brain (fore-, mid-, and hindbrain)• Cecum• Cervix• Colon• Duodenum• Epididymes• Esophagus• Eyes, with optic nerve (fixed with formol alcohol preservative)• Heart• Identification; (retained in formalin; not processed for histology)• Ileum• Injection site(s) tissue. (Entire Tail)

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- Jejunum
- Kidneys
- Liver
- Lungs with bronchi
- Lymph nodes, mandibular and mesenteric
- Mammary gland (when present in regular abdominal skin section, include nipple and surrounding tissue)
- Ovaries
- Pancreas
- Pituitary gland
- Prostate
- Rectum
- Salivary gland, mandibular
- Sciatic nerve
- Seminal vesicle
- Skeletal muscle
- Skin, ventral abdomen, taken with mammary gland
- Spinal cord retained within spinal column (thoracolumbar only)
- Spleen
- Stomach (include nonglandular stomach)
- Testes
- Thymus
- Thyroid/parathyroid glands
- Trachea
- Urinary bladder
- Uterus
- Vagina

**Final Body/
Organ Weights:**

Body weight was recorded on the day of necropsy for body to organ weight ratios. The following organs were weighed. Paired organs were weighed together.

- Adrenal glands
- Brain
- Heart
- Kidneys
- Liver
- Ovaries
- Spleen
- Testes, without epididymes
- Thymus

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E. Histopathologic Examination:

Tissues:	Tissues listed above were processed and evaluated for the following: <ul style="list-style-type: none">• All animals in the control Group 1 and high dose Group 2.
Tissue Sections:	Sections of the tissues were embedded in paraffin, cut approximately 5 μm thick, and stained with hematoxylin and eosin by VDx (Davis, CA), a histology laboratory qualified by SRI.
Evaluated by:	Ken Altera, DVM, PhD, DACVP of Westpath Corporation, a board-certified veterinary pathologist.
Method:	Each lesion was listed and coded by the most specific topographic and morphologic diagnoses, severity, and distribution, using Systematized Nomenclature of Medicine (SNOMED) and National Toxicology Program Toxicology Data Management System (TDMS) as guides. A four-step grading system (minimal, mild, moderate, and marked) was used to define gradable lesions for comparison between treated and control groups. Data was recorded and summarized using Provantis version 8.6.1.3. Records of gross findings for a specimen from postmortem observations were available to the pathologist when examining that specimen microscopically.

F. Evaluation of Data:

Parameters:	Mean and standard deviation were calculated for body weight, food consumption, clinical pathology, and organ weight data at each evaluation interval. Calculations were performed using Provantis version 8.6.1.3 and Labcat Clinical Pathology version 4.42.
Statistical Tests:	Body weights, organ weights and clinical pathology data were evaluated by one-way analysis of variance (ANOVA), followed by Dunnett's test (if the ANOVA is significant). All other numeric parameters were evaluated by Student <i>t</i> -test, unless

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specified otherwise. For clinical pathology data, values for parameters that were not within the detection threshold were not included in the statistical evaluation.

Criteria for Null Hypothesis Rejection: $p \leq 0.05$

G. Control of Bias

While evaluating the responses of the animals and conducting the analyses, the technical staff were aware of the treatment history of each animal and sample. Based on the relatively objective endpoints to be examined, bias is not expected to have influenced the results of the study.

H. Good Laboratory Practice Compliance

This study is intended to be submitted to and reviewed by the U.S. FDA or an equivalent regulatory agency, and this study therefore was performed in accordance with the U.S. FDA “Good Laboratory Practice for Nonclinical Laboratory Studies,” as described in 21 CFR Part 58, with the following exceptions:

- Various pre-initiation study activities (receipt and quarantine of animals and pre-initiation body weights) were performed prior to the approval of the protocol. These activities were conducted according to testing facility standard operating procedures (SOPs), but because they were conducted before the protocol was signed, they were considered by the FDA to not have been conducted in compliance with GLP requirements.
- Animal water, bedding, and food analysis were not performed under GLP compliance by the vendors.

I. Retention of Records and Study Samples

The original protocol, amendments, final report, raw data, supporting documents, and records, as well as all pathology materials (slides, blocks, and wet tissue specimens), specific to this study were retained and stored by SRI International. All records and materials will be maintained for a period of at least 1 year. At the end of the retention period, the Sponsor will be contacted for instructions regarding disposition of these materials.

V. RESULTS

A. Mortality/Morbidity and Clinical Observations

Clinical observations are summarized in Table 1. Mortality/morbidity and individual animal clinical observations are presented in Appendix C.

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All rats survived until their scheduled day of necropsy. Male (10 of 10) and female (6 of 10) rats in Group 2 that received 88.1 $\mu\text{g}/\text{kg}$ of ER176 exhibited ataxia (slight) immediately following dosing. These animals recovered by the next clinical observation at 2–4 hr post dose administration. One female rat (#036) that received 88.1 $\mu\text{g}/\text{kg}$ of ER176 exhibited hyperactivity (slight) immediately following dosing. Due to the ataxia clinical finding and in an attempt to establish the no observed adverse effect level (NOAEL), additional animals were evaluated for clinical observation after consultation with the Sponsor. An additional three groups of 10 male and 10 female rats were administered ER176, by iv tail vein injection, at 22.0, 44.1, or 88.1 $\mu\text{g}/\text{kg}$. While no clinical observations were noted in male or female rats treated with the follow-up dose of 88.1 $\mu\text{g}/\text{kg}$ of ER176 (Group 5), ataxia (slight) was observed immediately post-dose in one male rat (#065) in the 44.1 $\mu\text{g}/\text{kg}$ dose group. It is unclear why the ataxia finding was not replicated between the two 88.1 $\mu\text{g}/\text{kg}$ dose groups and why it was observed in the 44.1 $\mu\text{g}/\text{kg}$ dose group. The same chemical lot of ER176 was used to prepare dose solution, and the analytical evaluations of the dose solutions confirmed they were both at the nominal concentrations. A single occurrence of soft stool was observed in each of two male rats (#043 and 047) treated with 22.0 $\mu\text{g}/\text{kg}$ of ER176 within 1 hour post dose. Based on the sporadic nature of the soft stool in the 22.0 $\mu\text{g}/\text{kg}$ dose groups, as well as the lack of a dose response, these clinical observations are considered not to be related to ER176 treatment.

B. Body Weights

Body weight and weight gain are summarized in Tables 2 and 3, respectively. Individual animal body weights and weight gains are presented in Appendices D-1 and D-2, respectively.

No changes in body weight was observed in animals treated with 88.1 $\mu\text{g}/\text{kg}$ ER176 (Group 2) compared with the vehicle controls (Group 1). Animals in Groups 3–5 were from a different shipment, and therefore comparisons of body weights in Groups 3–5 with control animals in Group 1 are not appropriate. All dose groups exhibited normal body weight gains during the study.

C. Food Consumption

Food consumption is summarized in Table 4. Individual animal food consumption is presented in Appendix E.

Male and female rats treated with 88.1 $\mu\text{g}/\text{kg}$ of ER176 (Group 2) had slight but statistically significant increased food consumption on Days 1–2 (1.08-fold increase) and Days 6–7 (1.25-fold increase), respectively. Due to the sporadic nature of the changes along with the small magnitude of change these findings are not considered to be related to ER176 treatment.

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D. Clinical Pathology Evaluations

Hematology and clinical chemistry are summarized in Tables 5 and 6, respectively. Individual animal clinical pathology data are presented in Appendix F.

Hematology:

Female rats treated with 88.1 µg/kg of ER176 (Group 2) had slight but statistically significant reduced percent lymphocyte (PLY; 4%) levels and slight but statistically significant elevated mean corpuscular hemoglobin concentration (MCC; 1.02-fold increase) on Day 3 compared with controls. Male and female rats treated with 88.1 µg/kg of ER176 had slight but statistically significant elevated absolute eosinophil levels (AEO; 1.33-fold increase) on Day 15 compared with controls. These changes were all considered to be sporadic or of a magnitude commonly seen in laboratory rats under similar conditions, and therefore were not considered to be test article related.

Clinical Chemistry:

Male rats treated with 88.1 µg/kg of ER176 (Group 2) had slight but statistically significant elevated alkaline phosphatase (ALP; 1.21-fold increase) levels on Day 3 compared with controls. Female rats treated with 88.1 µg/kg of ER176 had slight but statistically significant elevated phosphorous (PHO; 1.17-fold increase) levels on Day 15 compared with controls. These changes were all considered to be sporadic or of a magnitude commonly seen in laboratory rats under similar conditions, and therefore were not considered to be test article related.

E. Gross Necropsy Findings

Necropsy observations are summarized in Table 7. Individual animal necropsy observations are presented in Appendix G.

One vehicle-treated male rat (#008) had a discolored (red) mandibular salivary gland on Day 15. One male rat (#022) that received 88.1 µg/kg of ER176 had an enlarged mandibular lymph node on Day 3.

Sporadic observations of discoloration and/or mottled pattern with foci were noted in lungs. These observations were most likely a secondary effect of euthanasia and were not considered to be test article related.

F. Organ Weights

Organ weights are summarized in Table 8. Individual animal organ weights are presented in Appendix H.

Female rats treated with 88.1 µg/kg of ER176 had significantly reduced adrenal gland weight (21%), adrenal/body weight ratio (19%), and adrenal/brain weight ratio (19%) compared with controls on Day 3. Due to the lack of microscopic changes in the

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adrenal glands and the inconsistency between males and female rats this finding is considered to be of minimal toxicological significance.

G. Histopathology

Histopathology is summarized in Table 9. The histopathology report is presented in Appendix I.

No histopathologic change attributed to ER176 was observed in the 88.1 $\mu\text{g}/\text{kg}$ dose group following iv administration at either the Day 3 Main group sacrifice or the Day 15 Recovery group sacrifice. Histopathologic findings were generally similar in the vehicle control and 88.1 $\mu\text{g}/\text{kg}$ dose groups, and were usually characteristic of background changes commonly seen in control rats of comparable age and gender.

Minor differences in nature, incidence, and/or severity of findings did exist between vehicle-control rats and those exposed to ER176. These differences were not attributed to ER176 and were not regarded as biologically meaningful. Such findings were generally similar to those commonly encountered as incidental background findings in control rats of comparable age and gender. They were not attributed to the test compound or regarded as biologically meaningful. Hemorrhage, especially in the brain, thymus, lung, and heart, was fresh/acute and was attributed to hypoxia during the euthanasia process and/or to manipulation of organs at necropsy. Such hemorrhage is common in euthanized rats.

VI. DISCUSSION AND CONCLUSIONS

In this study, a single dose of vehicle or ER176 (88.1 $\mu\text{g}/\text{kg}$) was administered by iv bolus to adult male and female Sprague Dawley rats; all animals survived to their scheduled sacrifice. There were no test article-related effects seen in the animals treated with 88.1 $\mu\text{g}/\text{kg}$ ER176 (Group 2) in body weights, food consumption, clinical pathology, gross necropsy, organ weights or histopathology, compared with the controls. However, the majority of male and female rats in the 88.1 $\mu\text{g}/\text{kg}$ dose group exhibited slight ataxia immediately following dosing. Due to this clinical finding and in an attempt to establish the no observed adverse effect level (NOAEL), additional animals treated with ER176, at 22.0, 44.1, or 88.1 $\mu\text{g}/\text{kg}$ were evaluated for clinical observation after consultation with the Sponsor. There were no test article-related clinical observations in the animals treated with 22.0 and 88.1 $\mu\text{g}/\text{kg}$ of ER176. However slight ataxia was observed in one male rat in the 44.1 $\mu\text{g}/\text{kg}$ dose group, immediately following dosing. It is not clear why animals in the two high-dose groups (88.1 $\mu\text{g}/\text{kg}$) responded differently to ER176 in Groups 2 and 5 in clinical observations immediately post dose administration. It may be due to animal-to-animal variations in different shipments. The same chemical lot of ER176 was used to prepare dose solution, and the analytical evaluations of the dose solutions confirmed they were both at the nominal concentrations.

In conclusion, a single dose of ER176 (22.0 $\mu\text{g}/\text{kg}$, 132.5 $\mu\text{g}/\text{m}^2$; 25 times the projected human dose) administered intravenously was well tolerated in rats and

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produced no treatment-related effects. Animals in the 44.1 and 88.1 $\mu\text{g}/\text{kg}$ treatment groups also tolerated the single dose administration, except that a slight and transient ataxia was observed. The NOAEL is considered to be 22.0 $\mu\text{g}/\text{kg}$ (132.5 $\mu\text{g}/\text{m}^2$; 25 times the projected human dose). The maximum tolerated dose (MTD) is considered to be greater than 88.1 $\mu\text{g}/\text{kg}$ (528.6 $\mu\text{g}/\text{m}^2$; 100 times the projected human dose).

Table 1: Clinical Observations Summary by Group
M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male	Day numbers relative to Start Date				
	Group 1 0	Group 2 88.1	Group 3 22.0	Group 4 44.1	Group 5 88.1
Ataxia					
Number of Observations	.	10	.	1	.
Number of Animals	.	10	.	1	.
Days from - to	.	1 1	.	1 1	.
Fecal Stain					
Number of Observations	.	.	1	.	.
Number of Animals	.	.	1	.	.
Days from - to	.	.	1 1	.	.
Hyperthermia					
Number of Observations	.	.	.	1	.
Number of Animals	.	.	.	1	.
Days from - to	.	.	.	1 1	.
Soft Stool					
Number of Observations	.	.	2	.	.
Number of Animals	.	.	2	.	.
Days from - to	.	.	1 1	.	.
Recovery Sacrifice					
Number of Observations	5	5	.	.	.
Number of Animals	5	5	.	.	.
Days from - to	15 15	15 15	.	.	.
Main Sacrifice					
Number of Observations	5	5	10	10	10
Number of Animals	5	5	10	10	10
Days from - to	3 3	3 3	3 3	3 3	3 3

General Footnote: . Not Applicable

Table 1 (concluded): Clinical Observations Summary by Group

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Day numbers relative to Start Date					
Sex: Female	Group 1 0	Group 2 88.1	Group 3 22.0	Group 4 44.1	Group 5 88.1
Ataxia					
Number of Observations	.	6	.	.	.
Number of Animals	.	6	.	.	.
Days from - to	.	1 1	.	.	.
Hyperactivity					
Number of Observations	.	1	.	.	.
Number of Animals	.	1	.	.	.
Days from - to	.	1 1	.	.	.
Recovery Sacrifice					
Number of Observations	5	5	.	.	.
Number of Animals	5	5	.	.	.
Days from - to	15 15	15 15	.	.	.
Main Sacrifice					
Number of Observations	5	5	10	10	10
Number of Animals	5	5	10	10	10
Days from - to	3 3	3 3	3 3	3 3	3 3

General Footnote: . Not Applicable

Table 2: Body Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male		Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV	Group 3 22.0 ug/kg IV	Group 4 44.1 ug/kg IV
Day(s) Relative to Start Date					
1	Mean	276.0	279.5	250.3	249.9
	SD	8.6	6.7	7.1	5.6
	N	10	10	10	10
3	Mean	284.5	290.5	262.3	266.1
	SD	10.9	8.4	10.9	6.6
	N	10	10	10	10
15	Mean	347.6	359.4	-	-
	SD	28.6	18.2	-	-
	N	5	5	-	-

Statistical Test: Anova & Dunnett's Transformation: Automatic

General Footnote: [- Not Applicable]

1 [I - Automatic Transformation: Identity (No Transformation)]

Table 2 (continued): Body Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Body Weight (g)

Sex: Male		Group 5 88.1 ug/kg IV
Day(s) Relative to Start Date		
1	Mean SD N	250.5 6.2 10
3	Mean SD N	266.6 7.4 10
15	Mean SD N	- - -

Statistical Test: Anova & Dunnett's Transformation: Automatic

General Footnote: [- Not Applicable]

Table 2 (continued): Body Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Body Weight (g)		Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV	Group 3 22.0 ug/kg IV	Group 4 44.1 ug/kg IV
Sex: Female					
Day(s) Relative to Start Date					
1	Mean	187.1 I ¹	181.9	173.1	174.7
	SD	5.3	6.7	9.0	8.0
	N	10	10	10	10
3	Mean	190.9 I ¹	187.3	178.6	179.6
	SD	5.3	7.4	7.4	8.6
	N	10	10	10	10
15	Mean	228.6 I ¹	224.8	-	-
	SD	16.9	5.5	-	-
	N	5	5	-	-

Statistical Test: Anova & Dunnett's Transformation: Automatic

General Footnote: [- Not Applicable]

1 [I - Automatic Transformation: Identity (No Transformation)]

Table 2 (concluded): Body Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Body Weight (g)

Sex: Female		Group 5 88.1 ug/kg IV
Day(s) Relative to Start Date		
1	Mean SD N	173.8 8.1 10
3	Mean SD N	180.8 9.0 10
15	Mean SD N	- - -

Statistical Test: Anova & Dunnett's Transformation: Automatic

General Footnote: [- Not Applicable]

Table 3: Body Weight Changes Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Absolute Weight Gain (g)		Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV	Group 3 22.0 ug/kg IV	Group 4 44.1 ug/kg IV
Sex: Male	Day(s) Relative to Start Date				
1 → 3	Mean	8.5 ¹¹	11.0	12.0	16.2
	SD	5.7	5.5	9.0	3.2
	N	10	10	10	10
3 → 15	Mean	66.6 ¹¹	72.8	-	-
	SD	17.9	14.8	-	-
	N	5	5	-	-

Statistical Test: Anova & Dunnett's Transformation: Automatic

General Footnote: [- Not Applicable]

1 [I - Automatic Transformation: Identity (No Transformation)]

Table 3 (continued): Body Weight Changes Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Absolute Weight Gain (g)

Sex: Male		Group 5 88.1 ug/kg IV
Day(s) Relative to Start Date		
1 → 3	Mean SD N	16.1 8.7 10
3 → 15	Mean SD N	- - -

Statistical Test: Anova & Dunnett's Transformation: Automatic

General Footnote: [- Not Applicable]

Table 3 (continued): Body Weight Changes Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Absolute Weight Gain (g)

Sex: Female		Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV	Group 3 22.0 ug/kg IV	Group 4 44.1 ug/kg IV
Day(s) Relative to Start Date					
1 → 3	Mean SD N	3.8 R ¹ 2.6 10	5.4 6.3 10	5.5 4.9 10	4.9 6.9 10
3 → 15	Mean SD N	38.4 I ² 10.2 5	37.6 7.2 5	- - -	- - -

Statistical Test: Anova & Dunnett's Transformation: Automatic

General Footnote: [- Not Applicable]

1 [R - Automatic Transformation: Rank]

2 [I - Automatic Transformation: Identity (No Transformation)]

Table 3 (concluded): Body Weight Changes Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Absolute Weight Gain (g)

Sex: Female		Group 5 88.1 ug/kg IV
Day(s) Relative to Start Date		
1 → 3	Mean	7.0
	SD	4.8
	N	10
3 → 15	Mean	-
	SD	-
	N	-

Statistical Test: Anova & Dunnett's Transformation: Automatic

General Footnote: [- Not Applicable]

Table 4: Food Consumption Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Total Food Consumption (g)

Sex: Male		Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date			
1 → 2	Mean	23.30 R ¹	25.30 dd ²
	SD	1.26	1.07
	N	10	10
6 → 7	Mean	23.00 R ¹	23.60
	SD	0.46	0.82
	N	5	5
8 → 9	Mean	22.80 R ¹	22.00
	SD	0.64	0.91
	N	5	5

Statistical Test: Anova & Dunnett's Transformation: Automatic

1 [R - Automatic Transformation: Rank]

2 [dd - Test: Dunnett on Ranks 2 Sided p < 0.01]

Table 4 (concluded): Food Consumption Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Total Food Consumption (g)

Sex: Female		Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date			
1 → 2	Mean	14.30 R ¹	14.50
	SD	1.65	1.61
	N	10	10
6 → 7	Mean	14.80 R ¹	18.60 ddd ³
	SD	0.18	4.02
	N	5	5
8 → 9	Mean	18.00 I ²	18.20
	SD	0.46	1.19
	N	5	5

Statistical Test: Anova & Dunnett's Transformation: Automatic

1 [R - Automatic Transformation: Rank]

2 [I - Automatic Transformation: Identity (No Transformation)]

3 [ddd - Test: Dunnett on Ranks 2 Sided p < 0.001]

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Table 5
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 3, SEX: MALE

TEST(s): UNITS:	HCT %	HGB g/dL	RBC x10 ⁶ /uL	RDW %	WBC x10 ³ /uL
Group: Vehicle 0 ug/kg IV					
MEAN	42.4	13.4	6.58	12.5	10.62
SD	3.06	0.98	0.421	0.27	1.923
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	43.8	13.8	6.69	12.8	12.32
SD	1.74	0.64	0.181	0.51	1.181
N	5	5	5	5	5

WBC corrected for NRBC > 0

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Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 3, SEX: MALE

TEST(s): UNITS:	PNS %	PLY %	PMO %	PEO %	PBA %
Group: Vehicle 0 ug/kg IV					
MEAN	13.6	79.4	6.0	0.6	0.3
SD	2.50	6.17	4.70	0.37	0.19
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	16.4	78.4	4.1	0.7	0.4
SD	3.44	4.34	1.65	0.22	0.08
N	5	5	5	5	5

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Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 3, SEX: MALE

TEST(s):	ANS x1000/uL	ALY x1000/uL	AMO x1000/uL	AEO x1000/uL	ABA x1000/uL
<hr/>					
Group: Vehicle 0 ug/kg IV					
MEAN	1.44	8.43	0.64	0.06	0.03
SD	0.359	1.621	0.595	0.036	0.022
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	2.02	9.65	0.51	0.09	0.05
SD	0.504	0.977	0.230	0.034	0.004
N	5	5	5	5	5
<hr/>					

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Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 3, SEX: MALE

TEST(s): UNITS:	MCH pg	MCV fL	MCC g/dL	PLC x10 ³ /uL	MPV fL
Group: Vehicle 0 ug/kg IV					
MEAN	20.4	64.4	31.7	870	7.1
SD	0.25	0.75	0.21	40.2	0.45
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	20.7	65.5	31.6	930	7.3
SD	0.71	1.85	0.21	240.3	0.40
N	5	5	5	5	5

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Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 3, SEX: MALE

TEST(s): UNITS:	REA $\times 10^9/L$	RET % RBC
Group: Vehicle 0 ug/kg IV		
MEAN	365.5	5.55
SD	18.67	0.630
N	5	5
Group: ER176 88.1 ug/kg IV		
MEAN	427.2	6.40
SD	82.28	1.348
N	5	5

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Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 3, SEX: FEMALE

TEST(s): UNITS:	HCT %	HGB g/dL	RBC x10 ⁶ /uL	RDW %	WBC x10 ³ /uL
Group: Vehicle 0 ug/kg IV					
MEAN	42.3	13.5	6.81	11.7	10.46
SD	1.41	0.39	0.162	0.28	2.026
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	42.9	14.0	6.85	11.5	8.79
SD	2.17	0.59	0.304	0.56	1.534
N	5	5	5	5	5

WBC corrected for NRBC > 0

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Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 3, SEX: FEMALE

TEST(s): UNITS:	PNS %	PLY %	PMO %	PEO %	PBA %
Group: Vehicle 0 ug/kg IV					
MEAN	7.4	89.5	2.4	0.4	0.3
SD	1.88	2.18	0.95	0.21	0.16
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	8.9	86.0*	4.2	0.7	0.3
SD	1.52	2.48	2.29	0.24	0.05
N	5	5	5	5	5

*-Significant Difference from Control P < .05

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Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 3, SEX: FEMALE

TEST(s):	ANS x1000/uL	ALY x1000/uL	AMO x1000/uL	AEO x1000/uL	ABA x1000/uL
UNITS:					
Group: Vehicle 0 ug/kg IV					
MEAN	0.79	9.35	0.25	0.04	0.03
SD	0.315	1.737	0.081	0.025	0.022
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	0.77	7.55	0.38	0.06	0.03
SD	0.138	1.330	0.224	0.023	0.008
N	5	5	5	5	5

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Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 3, SEX: FEMALE

TEST(s): UNITS:	MCH pg	MCV fL	MCC g/dL	PLC x10 ³ /uL	MPV fL
Group: Vehicle 0 ug/kg IV					
MEAN	19.8	62.1	32.0	949	7.0
SD	0.44	1.44	0.30	194.6	0.51
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	20.5	62.7	32.7*	885	7.4
SD	0.64	2.60	0.48	364.4	0.19
N	5	5	5	5	5

*-Significant Difference from Control P < .05

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 3, SEX: FEMALE

TEST(s): UNITS:	REA x10 ⁹ /L	RET % RBC
Group: Vehicle 0 ug/kg IV		
MEAN	277.9	4.07
SD	64.23	0.899
N	5	5
Group: ER176 88.1 ug/kg IV		
MEAN	246.8	3.62
SD	46.23	0.782
N	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 15, SEX: MALE

TEST(s):	HCT	HGB	RBC	RDW	WBC
UNITS:	%	g/dL	$\times 10^6/\mu L$	%	$\times 10^3/\mu L$
Group: Vehicle 0 ug/kg IV					
MEAN	46.8	15.3	7.83	11.4	10.53
SD	2.22	0.59	0.439	0.36	2.060
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	45.9	15.0	7.51	11.5	10.77
SD	2.16	0.65	0.393	0.35	2.077
N	5	5	5	5	5

WBC corrected for NRBC > 0

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 15, SEX: MALE

TEST(s): UNITS:	PNS %	PLY %	PMO %	PEO %	PBA %
Group: Vehicle 0 ug/kg IV					
MEAN	11.2	85.1	2.8	0.6	0.4
SD	1.49	2.59	1.46	0.15	0.16
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	10.8	86.2	1.7	0.8	0.5
SD	4.13	4.71	0.55	0.15	0.10
N	5	5	5	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 15, SEX: MALE

TEST(s):	ANS x1000/uL	ALY x1000/uL	AMO x1000/uL	AEO x1000/uL	ABA x1000/uL
<hr/>					
Group: Vehicle 0 ug/kg IV					
MEAN	1.16	8.99	0.29	0.06	0.05
SD	0.136	1.949	0.142	0.011	0.023
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	1.10	9.35	0.18	0.08**	0.05
SD	0.270	2.176	0.039	0.004	0.023
N	5	5	5	5	5

**-Significant Difference from Control P < .01

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 15, SEX: MALE

TEST(s): UNITS:	MCH pg	MCV fL	MCC g/dL	PLC x10 ³ /uL	MPV fL
Group: Vehicle 0 ug/kg IV					
MEAN	19.5	59.9	32.6	846	6.7
SD	0.45	1.05	0.38	81.8	0.38
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	20.0	61.3	32.6	840	7.1
SD	0.68	3.06	0.59	82.4	0.47
N	5	5	5	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 15, SEX: MALE

TEST(s):	REA x10 ⁹ /L	RET % RBC
Group: Vehicle 0 ug/kg IV		
MEAN	208.2	2.66
SD	30.38	0.356
N	5	5
Group: ER176 88.1 ug/kg IV		
MEAN	207.1	2.77
SD	60.51	0.801
N	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 15, SEX: FEMALE

TEST(s):	HCT	HGB	RBC	RDW	WBC
UNITS:	%	g/dL	$\times 10^6/\mu L$	%	$\times 10^3/\mu L$
Group: Vehicle 0 ug/kg IV					
MEAN	41.9	13.9	7.28	11.1	10.02
SD	2.29	0.88	0.487	0.35	1.991
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	43.0	14.4	7.31	10.8	10.41
SD	1.51	0.53	0.281	0.29	1.753
N	5	5	5	5	5

WBC corrected for NRBC > 0

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 15, SEX: FEMALE

TEST(s): UNITS:	PNS %	PLY %	PMO %	PEO %	PBA %
Group: Vehicle 0 ug/kg IV					
MEAN	8.8	88.0	2.3	0.6	0.4
SD	1.73	2.13	0.51	0.08	0.10
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	10.6	86.2	2.0	0.8	0.4
SD	3.58	3.78	0.90	0.18	0.04
N	5	5	5	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 15, SEX: FEMALE

TEST(s):	ANS x1000/uL	ALY x1000/uL	AMO x1000/uL	AEO x1000/uL	ABA x1000/uL
<hr/>					
Group: Vehicle 0 ug/kg IV					
MEAN	0.90	8.80	0.23	0.06	0.04
SD	0.314	1.667	0.066	0.016	0.012
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	1.09	8.99	0.21	0.08*	0.04
SD	0.415	1.631	0.094	0.005	0.011
N	5	5	5	5	5

*-Significant Difference from Control P < .05

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 5 (continued)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 15, SEX: FEMALE

TEST(s): UNITS:	MCH pg	MCV fL	MCC g/dL	PLC x10³/uL	MPV fL
Group: Vehicle 0 ug/kg IV					
MEAN	19.1	57.6	33.2	806	7.1
SD	0.65	1.14	0.75	139.8	0.62
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	19.7	58.8	33.4	731	7.5
SD	0.65	2.13	0.33	210.7	0.47
N	5	5	5	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 5 (concluded)
CLINICAL PATHOLOGY SUMMARY-HEMATOLOGY
PERIOD: Day 15, SEX: FEMALE

TEST(s):	REA x10 ⁹ /L	RET % RBC
Group: Vehicle 0 ug/kg IV		
MEAN	175.8	2.46
SD	33.65	0.508
N	5	5
Group: ER176 88.1 ug/kg IV		
MEAN	181.3	2.50
SD	59.65	0.875
N	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 3, SEX: MALE

TEST(s): UNITS:	TBI mg/dL	CRE mg/dL	SOD mEq/L	POT mEq/L	CHL mEq/L
Group: Vehicle 0 ug/kg IV					
MEAN	NA	0.20	143	5.9	99
SD	NA	0.011	0.8	0.63	0.9
N	0	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	NA	0.19	143	6.5	99
SD	NA	0.018	1.7	0.40	1.5
N	0	5	5	5	5

NA-Not Applicable

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 3, SEX: MALE

TEST(s): UNITS:	CHO mg/dL	TRI mg/dL	GLU mg/dL	BUN mg/dL	AST U/L
Group: Vehicle 0 ug/kg IV					
MEAN	86	185	130	14	84
SD	14.0	77.0	14.7	1.8	11.7
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	98	163	128	14	86
SD	18.5	61.5	13.2	1.5	2.0
N	5	5	5	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 3, SEX: MALE

TEST(s): UNITS:	ALT U/L	ALP U/L	CAL mg/dL	PHO mg/dL	TPR g/dL
Group: Vehicle 0 ug/kg IV					
MEAN	51	326	12.1	10.8	6.1
SD	8.5	30.0	0.34	0.63	0.21
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	50	396*	12.4	11.0	6.1
SD	5.4	50.7	0.23	0.67	0.31
N	5	5	5	5	5

--Significant Difference from Control P < .05

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 3, SEX: MALE

TEST(s): UNITS:	ALB g/dL	AGR na	GLO g/dL
Group: Vehicle 0 ug/kg IV			
MEAN	4.1	2	2.0
SD	0.19	0.0	0.08
N	5	5	5
Group: ER176 88.1 ug/kg IV			
MEAN	4.1	2	2.1
SD	0.23	0.0	0.11
N	5	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 3, SEX: FEMALE

TEST(s): UNITS:	TBI mg/dL	CRE mg/dL	SOD mEq/L	POT mEq/L	CHL mEq/L
Group: Vehicle 0 ug/kg IV					
MEAN	NA	0.23	143	5.6	100
SD	NA	0.031	0.9	0.72	1.5
N	0	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	NA	0.23	143	5.3	99
SD	NA	0.036	0.8	0.79	1.8
N	0	5	5	5	5

NA-Not Applicable

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 3, SEX: FEMALE

TEST(s): UNITS:	CHO mg/dL	TRI mg/dL	GLU mg/dL	BUN mg/dL	AST U/L
Group: Vehicle 0 ug/kg IV					
MEAN	97	65	145	16	82
SD	10.6	26.8	34.9	2.2	9.2
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	100	90	148	16	76
SD	12.1	24.8	40.0	2.3	8.3
N	5	5	5	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 3, SEX: FEMALE

TEST(s):	ALT	ALP	CAL	PHO	TPR
UNITS:	U/L	U/L	mg/dL	mg/dL	g/dL
Group: Vehicle 0 ug/kg IV					
MEAN	42	252	12.5	11.6	6.4
SD	6.1	35.2	0.41	0.89	0.23
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	40	200	12.6	11.0	6.6
SD	1.1	48.8	0.63	0.59	0.19
N	5	5	5	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 3, SEX: FEMALE

TEST(s): UNITS:	ALB g/dL	AGR na	GLO g/dL
Group: Vehicle 0 ug/kg IV			
MEAN	4.5	2	1.9
SD	0.32	0.5	0.15
N	5	5	5
Group: ER176 88.1 ug/kg IV			
MEAN	4.7	3	1.8
SD	0.19	0.4	0.09
N	5	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 15, SEX: MALE

TEST(s): UNITS:	TBI mg/dL	CRE mg/dL	SOD mEq/L	POT mEq/L	CHL mEq/L
Group: Vehicle 0 ug/kg IV					
MEAN	NA	0.25	144	6.1	98
SD	NA	0.031	1.2	0.84	0.9
N	0	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	NA	0.25	144	5.7	99
SD	NA	0.038	0.8	0.85	0.8
N	0	5	5	5	5

NA-Not Applicable

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 15, SEX: MALE

TEST(s): UNITS:	CHO mg/dL	TRI mg/dL	GLU mg/dL	BUN mg/dL	AST U/L
Group: Vehicle 0 ug/kg IV					
MEAN	81	188	125	16	81
SD	9.9	37.1	8.0	0.9	7.9
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	87	190	159	15	76
SD	13.6	57.1	47.9	1.1	10.7
N	5	5	5	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 15, SEX: MALE

TEST(s): UNITS:	ALT U/L	ALP U/L	CAL mg/dL	PHO mg/dL	TPR g/dL
Group: Vehicle 0 ug/kg IV					
MEAN	50	271	11.8	8.5	6.6
SD	6.0	39.9	0.29	0.73	0.23
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	56	262	12.4	9.0	6.3
SD	7.6	33.2	0.52	0.44	0.19
N	5	5	5	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 15, SEX: MALE

TEST(s): UNITS:	ALB g/dL	AGR na	GLO g/dL
Group: Vehicle 0 ug/kg IV			
MEAN	4.3	2	2.3
SD	0.18	0.0	0.28
N	5	5	5
Group: ER176 88.1 ug/kg IV			
MEAN	4.2	2	2.2
SD	0.15	0.0	0.19
N	5	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 15, SEX: FEMALE

TEST(s): UNITS:	TBI mg/dL	CRE mg/dL	SOD mEq/L	POT mEq/L	CHL mEq/L
Group: Vehicle 0 ug/kg IV					
MEAN	NA	0.27	143	5.8	99
SD	NA	0.027	0.9	0.30	1.6
N	0	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	NA	0.29	145	5.4	100
SD	NA	0.047	1.1	0.41	1.3
N	0	5	5	5	5

NA-Not Applicable

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 15, SEX: FEMALE

TEST(s): UNITS:	CHO mg/dL	TRI mg/dL	GLU mg/dL	BUN mg/dL	AST U/L
Group: Vehicle 0 ug/kg IV					
MEAN	100	133	126	20	75
SD	9.6	82.7	9.8	2.8	9.5
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	95	68	136	20	72
SD	11.0	27.9	13.8	3.9	2.9
N	5	5	5	5	5

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (continued)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 15, SEX: FEMALE

TEST(s): UNITS:	ALT U/L	ALP U/L	CAL mg/dL	PHO mg/dL	TPR g/dL
Group: Vehicle 0 ug/kg IV					
MEAN	47	177	12.1	7.5	6.6
SD	5.9	27.2	0.36	0.38	0.35
N	5	5	5	5	5
Group: ER176 88.1 ug/kg IV					
MEAN	43	214	12.1	8.8**	6.4
SD	6.7	55.9	0.34	0.69	0.44
N	5	5	5	5	5

**-Significant Difference from Control P < .01

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table 6 (concluded)
CLINICAL PATHOLOGY SUMMARY-CHEMISTRY
PERIOD: Day 15, SEX: FEMALE

TEST(s): UNITS:	ALB g/dL	AGR na	GLO g/dL
Group: Vehicle 0 ug/kg IV			
MEAN	4.6	2	2.0
SD	0.20	0.4	0.21
N	5	5	5
Group: ER176 88.1 ug/kg IV			
MEAN	4.4	2	1.9
SD	0.35	0.4	0.21
N	5	5	5

Table 7: Necropsy Observations Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1		Group 2		Group 1	
	0 ug/kg IV	88.1 ug/kg IV			0 ug/kg IV	88.1 ug/kg IV
Number of Animals:	5		5		5	
ADRENAL GLANDS						
Submitted	5	5			5	5
Normal	5	5			5	5
AORTA						
Submitted	5	5			5	5
Normal	5	5			5	5
BONE MARROW SMEAR, STERNUM						
CYTOTOLOGY						
Submitted	5	5			5	5
Normal	5	5			5	5
BONE, FEMUR WITH FEMORO-TIBIAL JOINT						
Submitted	5	5			5	5
Normal	5	5			5	5
BONE, STERNUM (MARROW HISTOLOGY)						
Submitted	5	5			5	5
Normal	5	5			5	5
BRAIN (FORE-, MID-, HINDBRAIN)						
Submitted	5	5			5	5
Normal	5	5			5	5
CERVIX						
Submitted	.	.			5	5
Normal	.	.			5	5
EPIDIDYMIDES						
Submitted	5	5			.	.
Normal	5	5			.	.
ESOPHAGUS						
Submitted	5	5			5	5
Normal	5	5			5	5
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL)						
Submitted	5	5			5	5
Normal	5	5			5	5
IDENTIFICATION						
Submitted	5	5			5	5
Normal	5	5			5	5
GROSS LESIONS						
Submitted	5	5			5	5
Normal	5	5			5	5

General Footnote: [. Not Applicable]

Table 7 (continued): Necropsy Observations Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1		Group 2		Group 1	
	0 ug/kg IV	88.1 ug/kg IV			0 ug/kg IV	88.1 ug/kg IV
Number of Animals:	5		5		5	
HEART						
Submitted	5	5			5	5
Normal	5	5			5	5
INJECTION SITE: TAIL, ENTIRE						
TAIL, ENTIRE : Submitted	5	5			5	5
TAIL, ENTIRE : Normal	5	5			5	5
INTESTINE, CECUM						
Submitted	5	5			5	5
Normal	5	5			5	5
INTESTINE, COLON						
Submitted	5	5			5	5
Normal	5	5			5	5
INTESTINE, DUODENUM						
Submitted	5	5			5	5
Normal	5	5			5	5
INTESTINE, ILEUM						
Submitted	5	5			5	5
Normal	5	5			5	5
INTESTINE, JEJUNUM						
Submitted	5	5			5	5
Normal	5	5			5	5
INTESTINE, RECTUM						
Submitted	5	5			5	5
Normal	5	5			5	5
KIDNEYS						
Submitted	5	5			5	5
Normal	5	5			5	5
LIVER						
Submitted	5	5			5	5
Normal	5	5			5	5
LUNGS WITH BRONCHI						
Submitted	5	5			5	5
Normal	5	4			5	5
Discolored; dark	0	1			0	0
LYMPH NODE, MESENTERIC						
Submitted	5	5			5	5
Normal	5	5			5	5

General Footnote: [. Not Applicable]

Table 7 (continued): Necropsy Observations Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV	Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV	Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Number of Animals:	5	5	5	5	5	5
LYMPH NODE, MANDIBULAR						
Submitted	5	5			5	5
Normal	5	4			5	5
Enlarged	0	1			0	0
MAMMARY GLANDS						
Submitted	5	5			5	5
Normal	5	5			5	5
SKELETAL MUSCLE						
Submitted	5	5			5	5
Normal	5	5			5	5
NERVE, SCIATIC						
Submitted	5	5			5	5
Normal	5	5			5	5
OVARIES						
Submitted	.	.			5	5
Normal	.	.			5	5
PANCREAS						
Submitted	5	5			5	5
Normal	5	5			5	5
PITUITARY GLAND						
Submitted	5	5			5	5
Normal	5	5			5	5
PROSTATE GLAND						
Submitted	5	5			.	.
Normal	5	5			.	.
SALIVARY GLAND, MANDIBULAR						
Submitted	5	5			5	5
Normal	5	5			5	5
SEMINAL VESICLES						
Submitted	5	5			.	.
Normal	5	5			.	.
SKIN, VENTRAL ABDOMEN						
Submitted	5	5			5	5
Normal	5	5			5	5
SPINAL CORD, THORACOLUMBAR						
Submitted	5	5			5	5
Normal	5	5			5	5

General Footnote: [. Not Applicable]

Table 7 (continued): Necropsy Observations Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1		Group 2		Group 1	
	0 ug/kg IV	88.1 ug/kg IV			0 ug/kg IV	88.1 ug/kg IV
Number of Animals:	5	5			5	5
SPLEEN						
Submitted	5	5			5	5
Normal	5	5			5	5
STOMACH, INCLUDING NONGLANDULAR						
Submitted	5	5			5	5
Normal	5	5			5	5
TESTES						
Submitted	5	5			.	.
Normal	5	5			.	.
THYMUS						
Submitted	5	5			5	5
Normal	5	5			5	5
THYROID/PARATHYROID GLANDS						
Submitted	5	5			5	5
Normal	5	5			5	5
TRACHEA						
Submitted	5	5			5	5
Normal	5	5			5	5
URINARY BLADDER						
Submitted	5	5			5	5
Normal	5	5			5	5
UTERUS						
Submitted	.	.			5	5
Normal	.	.			5	5
VAGINA						
Submitted	.	.			5	5
Normal	.	.			5	5

General Footnote: [. Not Applicable]

Table 7 (continued): Necropsy Observations Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
ADRENAL GLANDS						
Submitted	5	5			5	5
Normal	5	5			5	5
AORTA						
Submitted	5	5			5	5
Normal	5	5			5	5
BONE MARROW SMEAR, STERNUM						
CYTOTOLOGY						
Submitted	5	5			5	5
Normal	5	5			5	5
BONE, FEMUR WITH FEMORO-TIBIAL JOINT						
Submitted	5	5			5	5
Normal	5	5			5	5
BONE, STERNUM (MARROW HISTOLOGY)						
Submitted	5	5			5	5
Normal	5	5			5	5
BRAIN (FORE-, MID-, HINDBRAIN)						
Submitted	5	5			5	5
Normal	5	5			5	5
CERVIX						
Submitted	.	.			5	5
Normal	.	.			5	5
EPIDIDYMIDES						
Submitted	5	5			.	.
Normal	5	5			.	.
ESOPHAGUS						
Submitted	5	5			5	5
Normal	5	5			5	5
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL)						
Submitted	5	5			5	5
Normal	5	5			5	5
IDENTIFICATION						
Submitted	5	5			5	5
Normal	5	5			5	5
GROSS LESIONS						
Submitted	5	5			5	5

General Footnote: [. Not Applicable]

Table 7 (continued): Necropsy Observations Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1		Group 2		Group 1	
	0 ug/kg IV	88.1 ug/kg IV	0 ug/kg IV	88.1 ug/kg IV	0 ug/kg IV	88.1 ug/kg IV
Number of Animals:	5		5		5	
GROSS LESIONS (Continued...)						
Normal	5	5			5	5
HEART						
Submitted	5	5			5	5
Normal	5	5			5	5
INJECTION SITE: TAIL, ENTIRE						
TAIL, ENTIRE : Submitted	5	5			5	5
TAIL, ENTIRE : Normal	5	5			5	5
INTESTINE, CECUM						
Submitted	5	5			5	5
Normal	5	5			5	5
INTESTINE, COLON						
Submitted	5	5			5	5
Normal	5	5			5	5
INTESTINE, DUODENUM						
Submitted	5	5			5	5
Normal	5	5			5	5
INTESTINE, ILEUM						
Submitted	5	5			5	5
Normal	5	5			5	5
INTESTINE, JEJUNUM						
Submitted	5	5			5	5
Normal	5	5			5	5
INTESTINE, RECTUM						
Submitted	5	5			5	5
Normal	5	5			5	5
KIDNEYS						
Submitted	5	5			5	5
Normal	5	5			5	5
LIVER						
Submitted	5	5			5	5
Normal	5	5			5	5
LUNGS WITH BRONCHI						
Submitted	5	5			5	5
Normal	5	4			5	5
Mottled	0	1			0	0

General Footnote: [. Not Applicable]

Table 7 (continued): Necropsy Observations Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1		Group 2		Group 1	
	0 ug/kg IV	88.1 ug/kg IV	0 ug/kg IV	88.1 ug/kg IV	0 ug/kg IV	88.1 ug/kg IV
Number of Animals:	5		5		5	
LYMPH NODE, MESENTERIC						
Submitted	5	5			5	5
Normal	5	5			5	5
LYMPH NODE, MANDIBULAR						
Submitted	5	5			5	5
Normal	5	5			5	5
MAMMARY GLANDS						
Submitted	5	5			5	5
Normal	5	5			5	5
SKELETAL MUSCLE						
Submitted	5	5			5	5
Normal	5	5			5	5
NERVE, SCIATIC						
Submitted	5	5			5	5
Normal	5	5			5	5
OVARIES						
Submitted	.	.			5	5
Normal	.	.			5	5
PANCREAS						
Submitted	5	5			5	5
Normal	5	5			5	5
PITUITARY GLAND						
Submitted	5	5			5	5
Normal	5	5			5	5
PROSTATE GLAND						
Submitted	5	5			.	.
Normal	5	5			.	.
SALIVARY GLAND, MANDIBULAR						
Submitted	5	5			5	5
Normal	4	5			5	5
Discolored; red	1	0			0	0
SEMINAL VESICLES						
Submitted	5	5			.	.
Normal	5	5			.	.
SKIN, VENTRAL ABDOMEN						
Submitted	5	5			5	5

General Footnote: [. Not Applicable]

Table 7 (concluded): Necropsy Observations Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1		Group 2		Group 1	
	0 ug/kg IV	88.1 ug/kg IV	0 ug/kg IV	88.1 ug/kg IV	0 ug/kg IV	88.1 ug/kg IV
Number of Animals:	5		5		5	
SKIN, VENTRAL ABDOMEN (Continued...)						
Normal	5	5			5	5
SPINAL CORD, THORACOLUMBAR						
Submitted	5	5			5	5
Normal	5	5			5	5
SPLEEN						
Submitted	5	5			5	5
Normal	5	5			5	5
STOMACH, INCLUDING NONGLANDULAR						
Submitted	5	5			5	5
Normal	5	5			5	5
TESTES						
Submitted	5	5			.	.
Normal	5	5			.	.
THYMUS						
Submitted	5	5			5	5
Normal	5	5			5	5
THYROID/PARATHYROID GLANDS						
Submitted	5	5			5	5
Normal	5	5			5	5
TRACHEA						
Submitted	5	5			5	5
Normal	5	5			5	5
URINARY BLADDER						
Submitted	5	5			5	5
Normal	5	5			5	5
UTERUS						
Submitted	.	.			5	5
Normal	.	.			5	5
VAGINA						
Submitted	.	.			5	5
Normal	.	.			5	5

General Footnote: [. Not Applicable]

Table 8: Organ Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male			Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date				
Adrenal Glands Wt (g)	3	Mean SD N	0.0422 R ¹ 0.0127 5	0.0426 0.0037 5
Brain Weight (g)	3	Mean SD N	1.9218 I ² 0.0742 5	1.8768 0.1640 5
Heart Weight (g)	3	Mean SD N	1.0314 I ² 0.0547 5	1.0748 0.0673 5
Kidneys Weight (g)	3	Mean SD N	2.2266 R ¹ 0.0358 5	2.3306 0.2009 5
Liver Weight (g)	3	Mean SD N	12.0882 L ³ 0.5247 5	12.2628 1.0699 5
Spleen Weight (g)	3	Mean SD N	0.6986 I ² 0.0911 5	0.6506 0.1757 5
Testes Weight (g)	3	Mean SD N	2.6534 I ² 0.1340 5	2.7830 0.2971 5
Thymus Weight (g)	3	Mean SD N	0.6988 I ² 0.0917 5	0.6976 0.1109 5
Adrenal/Body weight (%)	3	Mean SD N	0.0147 R ¹ 0.0045 5	0.0145 0.0012 5
Brain/Body weight (%)	3	Mean SD N	0.6684 R ¹ 0.0421 5	0.6372 0.0458 5

1 [R - Automatic Transformation: Rank]

2 [I - Automatic Transformation: Identity (No Transformation)]

3 [L - Automatic Transformation: Log]

Table 8 (continued): Organ Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male			Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date				
Heart/Body weight (%)	3	Mean SD N	0.3587 R ¹ 0.0258 5	0.3654 0.0262 5
Kidney/Body weight (%)	3	Mean SD N	0.7738 I ² 0.0251 5	0.7916 0.0629 5
Liver/Body weight (%)	3	Mean SD N	4.1966 R ¹ 0.0316 5	4.1653 0.3281 5
Spleen/Body weight (%)	3	Mean SD N	0.2424 I ² 0.0288 5	0.2219 0.0620 5
Testes/Body weight (%)	3	Mean SD N	0.9219 I ² 0.0481 5	0.9467 0.1117 5
Thymus/Body weight (%)	3	Mean SD N	0.2430 I ² 0.0343 5	0.2376 0.0420 5
Adrenal/Brain (%)	3	Mean SD N	2.2015 R ¹ 0.6682 5	2.2831 0.2805 5
Heart/Brain (%)	3	Mean SD N	53.6956 I ² 2.6931 5	57.5883 5.6636 5
Kidneys/Brain (%)	3	Mean SD N	115.9815 I ² 4.3230 5	124.5429 10.1771 5
Liver/Brain (%)	3	Mean SD N	630.2118 I ² 46.4889 5	655.8387 59.8426 5

1 [R - Automatic Transformation: Rank]

2 [I - Automatic Transformation: Identity (No Transformation)]

Table 8 (continued): Organ Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male			Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date				
Spleen/ Brain (%)	3	Mean SD N	36.3681 I ¹ 4.6703 5	35.3742 11.8976 5
Testes/ Brain (%)	3	Mean SD N	138.2428 I ¹ 8.9131 5	148.9689 17.8629 5
Thymus/ Brain (%)	3	Mean SD N	36.4730 I ¹ 5.4636 5	37.2175 5.7218 5

1 [I - Automatic Transformation: Identity (No Transformation)]

Table 8 (continued): Organ Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female			Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date				
Adrenal Glands Wt (g)	3	Mean SD N	0.0540 I ¹ 0.0081 5	0.0428 d ² 0.0040 5
Brain Weight (g)	3	Mean SD N	1.8484 I ¹ 0.0526 5	1.7956 0.0522 5
Heart Weight (g)	3	Mean SD N	0.7738 I ¹ 0.0693 5	0.8294 0.0958 5
Kidneys Weight (g)	3	Mean SD N	1.6408 I ¹ 0.0835 5	1.6882 0.1101 5
Liver Weight (g)	3	Mean SD N	8.6894 I ¹ 0.3346 5	8.8488 0.9499 5
Ovaries Weight (g)	3	Mean SD N	0.2174 R ³ 0.3007 5	0.0770 0.0119 5
Spleen Weight (g)	3	Mean SD N	0.4852 I ¹ 0.0664 5	0.5186 0.0563 5
Thymus Weight (g)	3	Mean SD N	0.6012 I ¹ 0.0781 5	0.5682 0.0931 5
Adrenal/Body weight (%)	3	Mean SD N	0.0282 I ¹ 0.0042 5	0.0229 d ² 0.0026 5
Brain/Body weight (%)	3	Mean SD N	0.9647 R ³ 0.0233 5	0.9612 0.0736 5

1 [I - Automatic Transformation: Identity (No Transformation)]

2 [d - Test: Dunnett 2 Sided p < 0.05]

3 [R - Automatic Transformation: Rank]

Table 8 (continued): Organ Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female			Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date				
Heart/Body weight (%)	3	Mean SD N	0.4040 I ¹ 0.0376 5	0.4437 0.0590 5
Kidney/Body weight (%)	3	Mean SD N	0.8563 I ¹ 0.0409 5	0.9005 0.0152 5
Liver/Body weight (%)	3	Mean SD N	4.5355 I ¹ 0.1821 5	4.7121 0.2639 5
Ovaries/Body weight (%)	3	Mean SD N	0.1129 R ² 0.1556 5	0.0412 0.0066 5
Spleen/Body weight (%)	3	Mean SD N	0.2532 I ¹ 0.0345 5	0.2775 0.0353 5
Thymus/Body weight (%)	3	Mean SD N	0.3136 I ¹ 0.0394 5	0.3024 0.0401 5
Adrenal/Brain (%)	3	Mean SD N	2.9222 I ¹ 0.4419 5	2.3816 d ³ 0.1765 5
Heart/Brain (%)	3	Mean SD N	41.9686 R ² 4.8179 5	46.2009 5.2511 5
Kidneys/Brain (%)	3	Mean SD N	88.8380 I ¹ 5.4346 5	94.1872 8.4526 5
Liver/Brain (%)	3	Mean SD N	470.1357 R ² 13.7503 5	494.1863 66.2384 5

1 [I - Automatic Transformation: Identity (No Transformation)]

2 [R - Automatic Transformation: Rank]

3 [d - Test: Dunnett 2 Sided p < 0.05]

Table 8 (continued): Organ Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female			Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date				
Ovaries/ Brain (%)	3	Mean SD N	11.5564 R ¹ 15.7926 5	4.2988 0.7225 5
Spleen/ Brain (%)	3	Mean SD N	26.2285 I ² 3.3734 5	28.8855 3.0526 5
Thymus/ Brain (%)	3	Mean SD N	32.5513 I ² 4.4300 5	31.7147 5.6892 5

¹ [R - Automatic Transformation: Rank]² [I - Automatic Transformation: Identity (No Transformation)]

Table 8 (continued): Organ Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male			Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date				
Adrenal Glands Wt (g)	15	Mean SD N	0.0480 I ¹ 0.0094 5	0.0510 0.0065 5
Brain Weight (g)	15	Mean SD N	1.9946 I ¹ 0.0712 5	1.9538 0.0806 5
Heart Weight (g)	15	Mean SD N	1.1984 I ¹ 0.1250 5	1.2008 0.0727 5
Kidneys Weight (g)	15	Mean SD N	2.6380 I ¹ 0.1536 5	2.6426 0.1678 5
Liver Weight (g)	15	Mean SD N	13.3182 I ¹ 1.9353 5	13.6144 0.9782 5
Spleen Weight (g)	15	Mean SD N	0.6480 I ¹ 0.1037 5	0.7202 0.1067 5
Testes Weight (g)	15	Mean SD N	3.1330 I ¹ 0.1132 5	3.2520 0.1193 5
Thymus Weight (g)	15	Mean SD N	0.5048 I ¹ 0.1507 5	0.5900 0.1475 5
Adrenal/Body weight (%)	15	Mean SD N	0.0140 I ¹ 0.0034 5	0.0142 0.0015 5
Brain/Body weight (%)	15	Mean SD N	0.5763 I ¹ 0.0421 5	0.5446 0.0333 5

Table 8 (continued): Organ Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male			Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date				
Heart/Body weight (%)	15	Mean SD N	0.3450 I ¹ 0.0260 5	0.3342 0.0151 5
Kidney/Body weight (%)	15	Mean SD N	0.7611 I ¹ 0.0454 5	0.7349 0.0148 5
Liver/Body weight (%)	15	Mean SD N	3.8173 I ¹ 0.2822 5	3.7875 0.1747 5
Spleen/Body weight (%)	15	Mean SD N	0.1855 I ¹ 0.0158 5	0.2012 0.0351 5
Testes/Body weight (%)	15	Mean SD N	0.9047 I ¹ 0.0541 5	0.9068 0.0597 5
Thymus/Body weight (%)	15	Mean SD N	0.1437 I ¹ 0.0337 5	0.1642 0.0397 5
Adrenal/Brain (%)	15	Mean SD N	2.4128 I ¹ 0.5097 5	2.6115 0.3329 5
Heart/Brain (%)	15	Mean SD N	60.0839 I ¹ 6.0436 5	61.4433 2.1846 5
Kidneys/Brain (%)	15	Mean SD N	132.3248 I ¹ 7.6618 5	135.3819 9.2834 5
Liver/Brain (%)	15	Mean SD N	667.0141 I ¹ 86.5467 5	696.5984 35.5423 5

Table 8 (continued): Organ Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male			Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date				
Spleen/ Brain (%)	15	Mean SD N	32.4253 4.6005 5	36.8134 4.9576 5
Testes/ Brain (%)	15	Mean SD N	157.1640 5.9661 5	166.7555 10.7630 5
Thymus/ Brain (%)	15	Mean SD N	25.2609 7.1396 5	30.0735 6.5131 5

1 [I - Automatic Transformation: Identity (No Transformation)]

Table 8 (continued): Organ Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female			Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date				
Adrenal Glands Wt (g)	15	Mean SD N	0.0656 I ¹ 0.0101 5	0.0574 0.0133 5
Brain Weight (g)	15	Mean SD N	1.8992 I ¹ 0.0235 5	1.9038 0.0391 5
Heart Weight (g)	15	Mean SD N	0.8050 I ¹ 0.0579 5	0.9188 0.1184 5
Kidneys Weight (g)	15	Mean SD N	1.7746 I ¹ 0.1544 5	1.7520 0.0849 5
Liver Weight (g)	15	Mean SD N	9.4188 I ¹ 1.1997 5	9.0338 0.8293 5
Ovaries Weight (g)	15	Mean SD N	0.0942 L ² 0.0147 5	0.0890 0.0161 5
Spleen Weight (g)	15	Mean SD N	0.5338 I ¹ 0.0798 5	0.5700 0.0754 5
Thymus Weight (g)	15	Mean SD N	0.5466 I ¹ 0.0848 5	0.5584 0.0729 5
Adrenal/Body weight (%)	15	Mean SD N	0.0287 I ¹ 0.0033 5	0.0255 0.0059 5
Brain/Body weight (%)	15	Mean SD N	0.8344 I ¹ 0.0632 5	0.8474 0.0325 5

1 [I - Automatic Transformation: Identity (No Transformation)]

2 [L - Automatic Transformation: Log]

Table 8 (continued): Organ Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female			Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date				
Heart/Body weight (%)	15	Mean SD N	0.3529 I ¹ 0.0239 5	0.4085 0.0488 5
Kidney/Body weight (%)	15	Mean SD N	0.7759 I ¹ 0.0182 5	0.7795 0.0369 5
Liver/Body weight (%)	15	Mean SD N	4.1085 I ¹ 0.2653 5	4.0152 0.3045 5
Ovaries/Body weight (%)	15	Mean SD N	0.0413 I ¹ 0.0069 5	0.0397 0.0077 5
Spleen/Body weight (%)	15	Mean SD N	0.2327 I ¹ 0.0190 5	0.2535 0.0333 5
Thymus/Body weight (%)	15	Mean SD N	0.2382 I ¹ 0.0218 5	0.2488 0.0364 5
Adrenal/Brain (%)	15	Mean SD N	3.4508 I ¹ 0.4991 5	3.0212 0.7340 5
Heart/Brain (%)	15	Mean SD N	42.3705 I ¹ 2.6977 5	48.3503 7.0181 5
Kidneys/Brain (%)	15	Mean SD N	93.4223 I ¹ 7.7100 5	92.1188 6.1510 5
Liver/Brain (%)	15	Mean SD N	495.8955 I ¹ 61.8907 5	474.8643 47.0592 5

Table 8 (concluded): Organ Weights Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female			Group 1 0 ug/kg IV	Group 2 88.1 ug/kg IV
Day(s) Relative to Start Date				
Ovaries/ Brain (%)	15	Mean SD N	4.9540 I ¹ 0.7166 5	4.6727 0.8285 5
Spleen/ Brain (%)	15	Mean SD N	28.0905 I ¹ 4.0072 5	29.9583 4.0933 5
Thymus/ Brain (%)	15	Mean SD N	28.7724 I ¹ 4.3582 5	29.2980 3.4311 5

1 [I - Automatic Transformation: Identity (No Transformation)]

Table 9: Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female			
	Group 1		Group 2		Group 1		Group 2	
	0 ug/kg IV	88.1 ug/kg IV	0 ug/kg IV	88.1 ug/kg IV	5	5	5	5
Number of Animals:					5	5	5	5
ADRENAL GLANDS								
Examined	5	5			5	5		
Normal	4	5			5	5		
cortex; Hypertrophy; nodular, few	1	0			0	0		
.... minimal	1	0			0	0		
.... mild	0	0			0	0		
AORTA								
Examined	5	5			5	5		
Normal	5	5			5	5		
BONE MARROW SMEAR, STERNUM								
CYTOTOLOGY								
Examined	5	5			5	5		
Normal	5	5			5	5		
Not Examined: No Section	0	0			0	0		
BONE, FEMUR WITH FEMORO-TIBIAL JOINT								
Examined	5	5			5	5		
Normal	5	5			5	5		
BONE, STERNUM								
Examined	5	5			5	5		
Normal	5	5			5	5		
BONE, STERNUM (MARROW HISTOLOGY)								
Examined	5	5			5	5		
Normal	4	5			5	5		
Myelofibrosis; focal	1	0			0	0		
.... mild	1	0			0	0		
BRAIN (FORE-, MID-, HINDBRAIN)								
Examined	5	5			5	5		
Normal	0	0			1	1		
Hemorrhage; acute, multifocal	5	5			4	4		
.... minimal	4	5			2	3		
.... mild	1	0			2	1		
ventricle; Dilation	1	3			1	0		
.... mild	1	3			1	0		
CERVIX								
Examined	.	.			5	5		
Normal	.	.			5	5		

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
EPIDIDYMIDES						
Examined	5	5			.	.
Normal	5	2			.	.
Aspermia	0	1			.	.
.... present	0	1			.	.
duct; lumen; Debris; diffuse	0	1			.	.
.... mild	0	1			.	.
duct; lumen; Debris; few	0	1			.	.
.... minimal	0	1			.	.
duct; lumen; Hypocellularity; spermatozoal	0	2			.	.
.... mild	0	1			.	.
.... marked	0	1			.	.
ESOPHAGUS						
Examined	5	5			5	5
Normal	5	5			5	5
submucosa; Inflammation; focal	0	0			0	0
.... minimal	0	0			0	0
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL)						
Examined	5	5			5	5
Normal	4	4			1	3
periocular; Hemorrhage; acute, focal	0	1			2	0
.... mild	0	1			2	0
Inflammation; multifocal	0	0			1	0
.... minimal	0	0			1	0
periocular; Inflammation; few	0	1			0	2
.... minimal	0	1			0	2
retina; Dysplasia; few	0	0			2	0
.... minimal	0	0			2	0
.... mild	0	0			0	0
retina; Dysplasia; focal	1	0			0	0
.... minimal	1	0			0	0
retina; Dysplasia; multifocal	0	0			0	0
.... mild	0	0			0	0
HEART						
Examined	5	5			5	5

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
HEART (Continued...)						
Normal	0	0			1	1
Hemorrhage; acute, few	5	5			4	1
.... minimal	5	5			4	1
.... mild	0	0			0	0
Inflammation; few	0	0			0	1
.... minimal	0	0			0	1
Inflammation; focal	0	0			0	2
.... minimal	0	0			0	2
Inflammation; multifocal	0	0			0	0
.... mild	0	0			0	0
epicardium; Inflammation; focal	0	0			0	1
.... minimal	0	0			0	1
Epicarditis; focal	0	0			0	0
.... minimal	0	0			0	0
INJECTION SITE: TAIL, ENTIRE						
TAIL, ENTIRE : Examined	5	5			5	4
TAIL, ENTIRE : Normal	5	4			5	2
TAIL, ENTIRE : Not Examined: Lost At Necropsy	0	0			0	1
TAIL, ENTIRE : Not Examined: Not Collected	0	0			0	0
TAIL, ENTIRE : perivascular; Hemorrhage; acute, focal	0	1			0	0
.... minimal	0	1			0	0
TAIL, ENTIRE : perivascular; Inflammation; focal	0	1			0	2
.... minimal	0	1			0	1
.... mild	0	0			0	1
TAIL, ENTIRE : vein; Degeneration; focal	0	0			0	1
.... moderate	0	0			0	1
INTESTINE, CECUM						
Examined	5	5			5	5
Normal	2	0			2	3
mucosa; Congestion; multifocal	0	1			0	0
.... mild	0	1			0	0
submucosa; Congestion; few	1	2			0	2

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5		5	
INTESTINE, CECUM (Continued...)						
.... mild	1	2			0	2
submucosa; Edema; diffuse	2	1			2	1
.... mild	2	1			2	1
submucosa; Edema; focal	0	0			0	0
.... mild	0	0			0	0
submucosa; Edema; multifocal	1	3			1	1
.... mild	1	3			1	1
INTESTINE, COLON						
Examined	5	4			5	5
Normal	5	4			5	5
Not Examined: No Section	0	1			0	0
submucosa; Congestion; multifocal	0	0			0	0
.... mild	0	0			0	0
submucosa; Edema; multifocal	0	0			0	0
.... mild	0	0			0	0
INTESTINE, DUODENUM						
Examined	5	5			5	5
Normal	5	5			5	5
INTESTINE, ILEUM						
Examined	5	5			5	5
Normal	5	5			5	5
INTESTINE, JEJUNUM						
Examined	5	5			5	5
Normal	5	5			5	5
INTESTINE, RECTUM						
Examined	5	5			5	5
Normal	5	4			5	5
Not Examined: No Section	0	0			0	0
submucosa; Congestion; few	0	1			0	0
.... mild	0	1			0	0
KIDNEYS						
Examined	5	5			5	5
Normal	0	1			1	0
Cast; few	0	0			0	0
.... minimal	0	0			0	0

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
KIDNEYS (Continued...)						
Fibrosis; focal	1	0			1	1
.... minimal	1	0			1	1
.... mild	0	0			0	0
Inflammation; few	1	2			2	1
.... minimal	1	1			1	1
.... mild	0	1			1	0
Inflammation; focal	0	0			0	1
.... minimal	0	0			0	1
Inflammation; multifocal	0	0			0	0
.... minimal	0	0			0	0
Mineralization; few	0	0			0	2
.... minimal	0	0			0	2
Mineralization; focal	0	1			0	1
.... minimal	0	1			0	1
epithelium; tubule; Regeneration; few	2	0			0	1
.... minimal	2	0			0	1
epithelium; tubule; Regeneration; focal	1	0			0	2
.... minimal	1	0			0	2
epithelium; tubule; Regeneration; multifocal	2	3			2	1
.... minimal	2	3			2	1
tubule; epithelium; Regeneration; multifocal	0	0			2	0
.... mild	0	0			2	0
Cyst; few	0	0			0	1
.... minimal	0	0			0	1
.... mild	0	0			0	0
Cyst; focal	0	0			1	1
.... minimal	0	0			1	1
Dilation	0	0			0	0
.... mild	0	0			0	0
LIVER						
Examined	5	5			5	5
Hematopoiesis; few	2	0			1	1
.... minimal	2	0			0	1
.... mild	0	0			1	0

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female			
	Group 1		Group 2		Group 1		Group 2	
	0 ug/kg IV	88.1 ug/kg IV	0 ug/kg IV	88.1 ug/kg IV	5	5	5	5
Number of Animals:								
LIVER (Continued..)								
Hematopoiesis; multifocal	0	0			0	0		
.... mild	0	0			0	0		
periportal; Inflammation; few	1	4			4	3		
.... minimal	1	3			2	3		
.... mild	0	1			2	0		
periportal; Inflammation; multifocal	1	0			0	1		
.... minimal	1	0			0	1		
hepatocyte; Mitosis Increased; widespread	5	5			1	1		
.... minimal	0	0			1	0		
.... mild	1	2			0	1		
.... moderate	3	2			0	0		
.... marked	1	1			0	0		
hepatocyte; cytoplasm; Vacuolation; diffuse	2	3			5	3		
.... minimal	0	0			0	1		
.... mild	1	3			2	1		
.... moderate	1	0			3	1		
hepatocyte; cytoplasm; Vacuolation; multifocal	3	1			0	1		
.... minimal	0	0			0	0		
.... mild	1	0			0	0		
.... moderate	2	1			0	1		
hepatocyte; cytoplasm; Fatty Infiltration; diffuse	0	0			0	1		
.... minimal	0	0			0	1		
hepatocyte; cytoplasm; Fatty Infiltration; multifocal	0	0			1	0		
.... minimal	0	0			0	0		
.... mild	0	0			1	0		
hepatocyte; cytoplasm; Inclusion; eosinophilic, multifocal	0	0			0	0		
.... mild	0	0			0	0		
LUNGS WITH BRONCHI								
Examined	5	5			5	5		
alveolus; Hemorrhage; acute, multifocal	5	5			5	5		
.... minimal	0	1			3	3		
.... mild	5	3			2	2		
.... moderate	0	1			0	0		

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female			
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV	
	Number of Animals:		5	5	5		5	
LUNGS WITH BRONCHI (Continued..)								
peribronchiolar; Hemorrhage; acute, few	0	2			0	0		
.... minimal	0	2			0	0		
peribronchiolar; Hemorrhage; acute, multifocal	0	1			0	0		
.... mild	0	1			0	0		
perivascular; Hemorrhage; acute, few	4	3			3	5		
.... minimal	3	2			3	4		
.... mild	1	1			0	1		
perivascular; Hemorrhage; acute, multifocal	0	2			0	0		
.... mild	0	1			0	0		
.... moderate	0	1			0	0		
alveolus; macrophage; Proliferation; diffuse	0	1			0	0		
.... mild	0	1			0	0		
alveolus; macrophage; Proliferation; few	0	0			0	0		
.... minimal	0	0			0	0		
alveolus; macrophage; Proliferation; multifocal	1	1			2	1		
.... mild	1	1			2	1		
macrophage; alveolus; Proliferation; multifocal	4	3			3	4		
.... minimal	4	3			3	4		
alveolus; Edema; multifocal	0	1			0	0		
.... mild	0	1			0	0		
perivascular; Edema; few	1	2			1	1		
.... minimal	1	2			1	1		
perivascular; Edema; multifocal	1	2			1	0		
.... minimal	0	1			0	0		
.... mild	1	1			1	0		
artery; Mineralization; focal	1	0			1	0		
.... minimal	1	0			1	0		
peribronchiolar; Inflammation; focal	1	0			0	0		
.... minimal	1	0			0	0		
perivascular; Inflammation; few	1	2			1	2		
.... minimal	1	2			1	2		
perivascular; Inflammation; multifocal	0	1			2	0		
.... mild	0	1			2	0		

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5		5	
LYMPH NODE, MESENTERIC						
Examined	5	5			5	5
Normal	3	3			5	4
Hemorrhage; acute, few	2	1			0	1
.... minimal	2	1			0	1
Hemorrhage; acute, multifocal	0	1			0	0
.... minimal	0	1			0	0
LYMPH NODE, MANDIBULAR						
Examined	5	5			5	5
Hemorrhage; acute, few	0	0			1	3
.... minimal	0	0			1	3
Hemorrhage; acute, multifocal	5	4			3	0
.... minimal	2	1			0	0
.... mild	3	1			3	0
.... moderate	0	2			0	0
Plasmacytosis	5	5			5	5
.... mild	2	2			3	2
.... moderate	3	3			2	2
.... marked	0	0			0	1
Hyperplasia; lymphoid	1	1			0	0
.... moderate	1	1			0	0
MAMMARY GLANDS						
Examined	2	2			5	5
Normal	2	1			5	5
Not Examined: Not Present	3	3			0	0
perivascular; Hemorrhage; acute, few	0	1			0	0
.... mild	0	1			0	0
SKELETAL MUSCLE						
Examined	5	5			5	5
Normal	5	5			5	5
NERVE, SCIATIC						
Examined	5	5			5	5
Normal	5	5			5	5
OVARIES						
Examined	.	.			5	5
Normal	.	.			4	5

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
OVARIES (Continued...)						
follicle; Cyst; few	.	.			1	0
.... mild	.	.			1	0
PANCREAS						
Examined	5	5			5	5
Normal	5	4			5	5
Inflammation; few	0	0			0	0
.... mild	0	0			0	0
periductal; Inflammation; few	0	0			0	0
.... minimal	0	0			0	0
periductal; Inflammation; focal	0	1			0	0
.... minimal	0	1			0	0
PARATHYROID GLAND						
Examined	5	5			4	5
Normal	5	5			4	5
Not Examined: Not Present	0	0			1	0
PITUITARY GLAND						
Examined	5	5			5	5
Normal	5	5			4	5
Cyst; few	0	0			1	0
.... minimal	0	0			1	0
Cyst; focal	0	0			0	0
.... minimal	0	0			0	0
PROSTATE GLAND						
Examined	5	5			.	.
Normal	4	4			.	.
Inflammation; multifocal	1	1			.	.
.... mild	1	1			.	.
SALIVARY GLAND, MANDIBULAR						
Examined	5	5			5	5
Normal	5	4			5	5
Hemorrhage; acute, few	0	0			0	0
.... minimal	0	0			0	0
acinar cell; cytoplasm; Inclusion; focal	0	1			0	0
.... moderate	0	1			0	0

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
SEMINAL VESICLES						
Examined	5	5			.	.
Normal	5	5			.	.
SKIN, VENTRAL ABDOMEN						
Examined	5	5			5	5
Normal	5	5			5	4
subcutaneous; Hemorrhage; acute, few	0	0			0	1
.... minimal	0	0			0	1
Acanthosis; focal	0	0			0	0
.... minimal	0	0			0	0
Hyperkeratosis; focal	0	0			0	0
.... minimal	0	0			0	0
Parakeratosis; few	0	0			0	0
.... minimal	0	0			0	0
dermis; Inflammation; few	0	0			0	0
.... minimal	0	0			0	0
SPINAL COLUMN						
Examined	4	5			5	5
Normal	4	5			5	5
SPINAL CORD, THORACOLUMBAR						
Examined	5	5			5	5
Normal	4	4			4	5
Hemorrhage; acute, few	0	1			1	0
.... minimal	0	1			1	0
Hemorrhage; acute, focal	1	0			0	0
.... minimal	1	0			0	0
SPLEEN						
Examined	5	5			5	5
Congestion	5	5			4	5
.... mild	4	5			2	4
.... moderate	1	0			2	1
Hematopoiesis	5	5			5	5
.... mild	3	0			5	5
.... moderate	2	4			0	0
.... marked	0	1			0	0

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female			
	Group 1		Group 2		Group 1		Group 2	
	0 ug/kg IV	88.1 ug/kg IV	0 ug/kg IV	88.1 ug/kg IV	5	5	5	5
Number of Animals:								
STOMACH, INCLUDING NONGLANDULAR								
Examined	5	5			5	5		
Normal	0	0			0	0		
mucosa; glandular; Hemorrhage; acute, few	0	0			0	0		
.... minimal	0	0			0	0		
non-glandular; epithelium; Hyperplasia; multifocal	0	1			0	0		
.... mild	0	1			0	0		
glandular; submucosa; Inflammation; diffuse	0	0			2	0		
.... mild	0	0			2	0		
submucosa; glandular; Inflammation; few	2	4			1	2		
.... minimal	2	4			1	2		
submucosa; glandular; Inflammation; multifocal	3	1			2	3		
.... minimal	1	0			0	0		
.... mild	2	1			2	3		
submucosa; non-glandular; Inflammation; few	1	3			2	3		
.... minimal	1	3			2	3		
submucosa; non-glandular; Inflammation; multifocal	0	0			0	0		
.... mild	0	0			0	0		
non-glandular; epithelium; Hyperkeratosis; multifocal	0	1			0	0		
.... mild	0	1			0	0		
non-glandular; epithelium; Inclusion; few	0	1			0	0		
.... minimal	0	1			0	0		
TESTES								
Examined	5	5			.	.		
Normal	4	5			.	.		
seminiferous tubule; Hemorrhage; acute, few	1	0			.	.		
.... minimal	1	0			.	.		
THYMUS								
Examined	5	5			5	5		
Normal	1	1			1	2		
Hemorrhage; acute, few	2	3			4	1		
.... minimal	2	3			4	1		
.... mild	0	0			0	0		

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female			
	Group 1		Group 2		Group 1		Group 2	
	0 ug/kg IV	88.1 ug/kg IV	0 ug/kg IV	88.1 ug/kg IV	0	5	0	5
Number of Animals:	5	5			5	5		
THYMUS (Continued...)								
Hemorrhage; acute, focal	0	0			0	1		
.... minimal	0	0			0	1		
Hemorrhage; acute, multifocal	2	1			0	1		
.... minimal	2	0			0	1		
.... mild	0	1			0	0		
THYROID GLAND								
Examined	5	5			5	5		
Normal	4	4			3	4		
Cyst; ultimobranchial, few	0	0			2	1		
.... minimal	0	0			1	1		
.... mild	0	0			1	0		
Cyst; ultimobranchial, focal	1	1			0	0		
.... minimal	1	1			0	0		
Inflammation; focal	0	0			0	0		
.... minimal	0	0			0	0		
TRACHEA								
Examined	5	5			5	5		
mucosa; Hemorrhage; acute, few	0	1			0	0		
.... minimal	0	1			0	0		
.... mild	0	0			0	0		
mucosa; Hemorrhage; acute, focal	0	0			0	0		
.... mild	0	0			0	0		
mucosa; Hemorrhage; acute, multifocal	0	1			0	0		
.... mild	0	1			0	0		
mucosa; Hemorrhage; few	0	0			1	0		
.... minimal	0	0			1	0		
mucosa; Inflammation; multifocal	5	5			5	5		
.... minimal	0	1			0	1		
.... mild	5	3			5	4		
.... moderate	0	1			0	0		
mucosa; glands; Dilation; multifocal	5	5			4	5		
.... minimal	0	0			0	0		
.... mild	2	2			2	1		
.... moderate	3	3			2	4		

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female			
	Group 1		Group 2		Group 1		Group 2	
	0 ug/kg IV	88.1 ug/kg IV	0 ug/kg IV	88.1 ug/kg IV	5	5	5	5
Number of Animals:								
TRACHEA (Continued...)								
.... marked	0	0			0	0		
URINARY BLADDER								
Examined	5	5			5	4		
Normal	5	5			5	4		
Not Examined: No Section	0	0			0	1		
submucosa; Edema; diffuse	0	0			0	0		
.... moderate	0	0			0	0		
submucosa; Congestion; multifocal	0	0			0	0		
.... mild	0	0			0	0		
UTERUS								
Examined	.	.			5	5		
Normal	.	.			4	4		
Dilation	.	.			1	1		
.... mild	.	.			0	1		
.... moderate	.	.			0	0		
.... marked	.	.			1	0		
VAGINA								
Examined	.	.			5	5		
Normal	.	.			5	5		

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice Number of Animals:	Male				Female			
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV	
	5	5	5	5	5	5	5	5
ADRENAL GLANDS								
Examined	5	5			5	5		
Normal	4	5			2	4		
cortex; Hypertrophy; nodular, few	1	0			3	1		
.... minimal	0	0			1	1		
.... mild	1	0			2	0		
AORTA								
Examined	5	5			5	5		
Normal	5	5			5	5		
BONE MARROW SMEAR, STERNUM								
CYTOTOLOGY								
Examined	5	5			5	4		
Normal	5	5			5	4		
Not Examined: No Section	0	0			0	1		
BONE, FEMUR WITH FEMORO-TIBIAL JOINT								
Examined	5	5			5	5		
Normal	5	5			5	5		
BONE, STERNUM								
Examined	5	5			5	5		
Normal	5	5			5	5		
BONE, STERNUM (MARROW HISTOLOGY)								
Examined	5	5			5	5		
Normal	5	5			5	5		
Myelofibrosis; focal	0	0			0	0		
.... mild	0	0			0	0		
BRAIN (FORE-, MID-, HINDBRAIN)								
Examined	5	5			5	5		
Normal	0	0			0	0		
Hemorrhage; acute, multifocal	5	5			5	5		
.... minimal	2	4			4	4		
.... mild	3	1			1	1		
ventricle; Dilation	0	2			3	2		
.... mild	0	2			3	2		
CERVIX								
Examined	.	.			5	5		
Normal	.	.			5	5		

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1		Group 2		Group 1	
	0 ug/kg IV	88.1 ug/kg IV	0 ug/kg IV	88.1 ug/kg IV	0 ug/kg IV	88.1 ug/kg IV
Number of Animals:	5		5		5	
EPIDIDYMIDES						
Examined	5	5			.	.
Normal	5	5			.	.
Aspermia	0	0			.	.
.... present	0	0			.	.
duct; lumen; Debris; diffuse	0	0			.	.
.... mild	0	0			.	.
duct; lumen; Debris; few	0	0			.	.
.... minimal	0	0			.	.
duct; lumen; Hypocellularity; spermatozoal	0	0			.	.
.... mild	0	0			.	.
.... marked	0	0			.	.
ESOPHAGUS						
Examined	5	5			5	5
Normal	5	5			4	5
submucosa; Inflammation; focal	0	0			1	0
.... minimal	0	0			1	0
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL)						
Examined	5	5			5	5
Normal	3	4			5	4
periocular; Hemorrhage; acute, focal	0	0			0	0
.... mild	0	0			0	0
Inflammation; multifocal	0	0			0	0
.... minimal	0	0			0	0
periocular; Inflammation; few	0	0			0	0
.... minimal	0	0			0	0
retina; Dysplasia; few	1	1			0	1
.... minimal	1	0			0	0
.... mild	0	1			0	1
retina; Dysplasia; focal	0	0			0	0
.... minimal	0	0			0	0
retina; Dysplasia; multifocal	1	0			0	0
.... mild	1	0			0	0
HEART						
Examined	5	5			5	5

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
HEART (Continued...)						
Normal	1	1			2	3
Hemorrhage; acute, few	4	2			2	2
.... minimal	4	2			1	2
.... mild	0	0			1	0
Inflammation; few	0	1			0	1
.... minimal	0	1			0	1
Inflammation; focal	1	0			0	0
.... minimal	1	0			0	0
Inflammation; multifocal	0	0			1	0
.... mild	0	0			1	0
epicardium; Inflammation; focal	0	0			0	0
.... minimal	0	0			0	0
Epicarditis; focal	0	1			0	0
.... minimal	0	1			0	0
INJECTION SITE: TAIL, ENTIRE						
TAIL, ENTIRE : Examined	5	5			5	4
TAIL, ENTIRE : Normal	5	5			5	4
TAIL, ENTIRE : Not Examined: Lost At Necropsy	0	0			0	0
TAIL, ENTIRE : Not Examined: Not Collected	0	0			0	1
TAIL, ENTIRE : perivascular; Hemorrhage; acute, focal	0	0			0	0
.... minimal	0	0			0	0
TAIL, ENTIRE : perivascular; Inflammation; focal	0	0			0	0
.... minimal	0	0			0	0
.... mild	0	0			0	0
TAIL, ENTIRE : vein; Degeneration; focal	0	0			0	0
.... moderate	0	0			0	0
INTESTINE, CECUM						
Examined	5	5			5	5
Normal	2	3			1	2
mucosa; Congestion; multifocal	0	1			0	0
.... mild	0	1			0	0
submucosa; Congestion; few	2	0			0	1

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice Number of Animals:	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	5	5	5	5	5	5
INTESTINE, CECUM (Continued...)						
.... mild	2	0			0	1
submucosa; Edema; diffuse	2	0			1	2
.... mild	2	0			1	2
submucosa; Edema; focal	0	0			1	0
.... mild	0	0			1	0
submucosa; Edema; multifocal	1	2			2	1
.... mild	1	2			2	1
INTESTINE, COLON						
Examined	5	5			5	5
Normal	5	5			5	4
Not Examined: No Section	0	0			0	0
submucosa; Congestion; multifocal	0	0			0	1
.... mild	0	0			0	1
submucosa; Edema; multifocal	0	0			0	1
.... mild	0	0			0	1
INTESTINE, DUODENUM						
Examined	5	5			5	5
Normal	5	5			5	5
INTESTINE, ILEUM						
Examined	5	5			5	5
Normal	5	5			5	5
INTESTINE, JEJUNUM						
Examined	5	5			5	5
Normal	5	5			5	5
INTESTINE, RECTUM						
Examined	4	5			5	5
Normal	4	5			5	5
Not Examined: No Section	1	0			0	0
submucosa; Congestion; few	0	0			0	0
.... mild	0	0			0	0
KIDNEYS						
Examined	5	5			5	5
Normal	3	1			2	1
Cast; few	0	0			0	1
.... minimal	0	0			0	1

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:	5	5	5	5	
KIDNEYS (Continued...)						
Fibrosis; focal	0	0			1	0
.... minimal	0	0			0	0
.... mild	0	0			1	0
Inflammation; few	1	0			0	0
.... minimal	1	0			0	0
.... mild	0	0			0	0
Inflammation; focal	0	0			0	0
.... minimal	0	0			0	0
Inflammation; multifocal	0	0			1	0
.... minimal	0	0			1	0
Mineralization; few	0	0			1	0
.... minimal	0	0			1	0
Mineralization; focal	0	0			0	0
.... minimal	0	0			0	0
epithelium; tubule; Regeneration; few	1	1			0	2
.... minimal	1	1			0	2
epithelium; tubule; Regeneration; focal	0	3			1	2
.... minimal	0	3			1	2
epithelium; tubule; Regeneration; multifocal	1	0			0	0
.... minimal	1	0			0	0
tubule; epithelium; Regeneration; multifocal	0	0			0	0
.... mild	0	0			0	0
Cyst; few	0	0			1	0
.... minimal	0	0			0	0
.... mild	0	0			1	0
Cyst; focal	0	0			0	0
.... minimal	0	0			0	0
Dilation	1	0			0	0
.... mild	1	0			0	0
LIVER						
Examined	5	5			5	5
Hematopoiesis; few	1	2			3	4
.... minimal	0	2			2	3
.... mild	1	0			1	1

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
LIVER (Continued..)						
Hematopoiesis; multifocal	1	0			0	0
.... mild	1	0			0	0
periportal; Inflammation; few	1	2			3	3
.... minimal	1	2			1	3
.... mild	0	0			2	0
periportal; Inflammation; multifocal	2	3			0	2
.... minimal	2	3			0	2
hepatocyte; Mitosis Increased; widespread	3	5			1	0
.... minimal	3	2			1	0
.... mild	0	2			0	0
.... moderate	0	1			0	0
.... marked	0	0			0	0
hepatocyte; cytoplasm; Vacuolation; diffuse	2	5			5	5
.... minimal	0	1			0	0
.... mild	1	4			4	5
.... moderate	1	0			1	0
hepatocyte; cytoplasm; Vacuolation; multifocal	3	0			0	0
.... minimal	1	0			0	0
.... mild	1	0			0	0
.... moderate	1	0			0	0
hepatocyte; cytoplasm; Fatty Infiltration; diffuse	0	0			0	0
.... minimal	0	0			0	0
hepatocyte; cytoplasm; Fatty Infiltration; multifocal	0	0			2	0
.... minimal	0	0			1	0
.... mild	0	0			1	0
hepatocyte; cytoplasm; Inclusion; eosinophilic, multifocal	1	0			0	0
.... mild	1	0			0	0
LUNGS WITH BRONCHI						
Examined	5	5			5	5
alveolus; Hemorrhage; acute, multifocal	5	5			5	5
.... minimal	2	5			1	4
.... mild	3	0			4	1
.... moderate	0	0			0	0

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice Number of Animals:	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	5	5	5	5	5	5
LUNGS WITH BRONCHI (Continued..)						
peribronchiolar; Hemorrhage; acute, few	0	0			0	0
.... minimal	0	0			0	0
peribronchiolar; Hemorrhage; acute, multifocal	0	0			0	0
.... mild	0	0			0	0
perivascular; Hemorrhage; acute, few	1	4			2	3
.... minimal	0	3			2	3
.... mild	1	1			0	0
perivascular; Hemorrhage; acute, multifocal	0	1			1	0
.... mild	0	1			1	0
.... moderate	0	0			0	0
alveolus; macrophage; Proliferation; diffuse	0	0			0	0
.... mild	0	0			0	0
alveolus; macrophage; Proliferation; few	0	0			1	0
.... minimal	0	0			1	0
alveolus; macrophage; Proliferation; multifocal	1	2			1	1
.... mild	1	2			1	1
macrophage; alveolus; Proliferation; multifocal	4	3			3	4
.... minimal	4	3			3	4
alveolus; Edema; multifocal	0	0			0	0
.... mild	0	0			0	0
perivascular; Edema; few	1	1			1	4
.... minimal	1	1			1	4
perivascular; Edema; multifocal	1	0			1	0
.... minimal	0	0			0	0
.... mild	1	0			1	0
artery; Mineralization; focal	1	2			1	1
.... minimal	1	2			1	1
peribronchiolar; Inflammation; focal	0	0			0	0
.... minimal	0	0			0	0
perivascular; Inflammation; few	0	0			0	2
.... minimal	0	0			0	2
perivascular; Inflammation; multifocal	0	0			2	0
.... mild	0	0			2	0

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5		5	
LYMPH NODE, MESENTERIC						
Examined	5	5			5	5
Normal	4	3			3	4
Hemorrhage; acute, few	1	1			2	1
.... minimal	1	1			2	1
Hemorrhage; acute, multifocal	0	1			0	0
.... minimal	0	1			0	0
LYMPH NODE, MANDIBULAR						
Examined	5	5			5	5
Hemorrhage; acute, few	1	1			2	3
.... minimal	1	1			2	3
Hemorrhage; acute, multifocal	4	3			2	1
.... minimal	0	1			1	0
.... mild	4	1			1	1
.... moderate	0	1			0	0
Plasmacytosis	5	5			5	5
.... mild	3	3			1	4
.... moderate	2	2			2	0
.... marked	0	0			2	1
Hyperplasia; lymphoid	0	0			0	0
.... moderate	0	0			0	0
MAMMARY GLANDS						
Examined	3	5			5	5
Normal	3	5			5	5
Not Examined: Not Present	2	0			0	0
perivascular; Hemorrhage; acute, few	0	0			0	0
.... mild	0	0			0	0
SKELETAL MUSCLE						
Examined	5	5			5	5
Normal	5	5			5	5
NERVE, SCIATIC						
Examined	5	5			5	5
Normal	5	5			5	5
OVARIES						
Examined	.	.			5	5
Normal	.	.			5	5

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
OVARIES (Continued...)						
follicle; Cyst; few	.	.			0	0
.... mild	.	.			0	0
PANCREAS						
Examined	5	5			5	5
Normal	4	5			4	4
Inflammation; few	1	0			0	0
.... mild	1	0			0	0
periductal; Inflammation; few	0	0			0	1
.... minimal	0	0			0	1
periductal; Inflammation; focal	0	0			1	0
.... minimal	0	0			1	0
PARATHYROID GLAND						
Examined	5	4			5	4
Normal	5	4			5	4
Not Examined: Not Present	0	1			0	1
PITUITARY GLAND						
Examined	5	5			5	5
Normal	5	5			5	4
Cyst; few	0	0			0	0
.... minimal	0	0			0	0
Cyst; focal	0	0			0	1
.... minimal	0	0			0	1
PROSTATE GLAND						
Examined	5	5			.	.
Normal	5	5			.	.
Inflammation; multifocal	0	0			.	.
.... mild	0	0			.	.
SALIVARY GLAND, MANDIBULAR						
Examined	5	5			5	5
Normal	4	5			5	5
Hemorrhage; acute, few	1	0			0	0
.... minimal	1	0			0	0
acinar cell; cytoplasm; Inclusion; focal	0	0			0	0
.... moderate	0	0			0	0

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
SEMINAL VESICLES						
Examined	5	5			.	.
Normal	5	5			.	.
SKIN, VENTRAL ABDOMEN						
Examined	5	5			5	5
Normal	5	4			5	3
subcutaneous; Hemorrhage; acute, few	0	0			0	0
.... minimal	0	0			0	0
Acanthosis; focal	0	1			0	2
.... minimal	0	1			0	2
Hyperkeratosis; focal	0	1			0	0
.... minimal	0	1			0	0
Parakeratosis; few	0	0			0	1
.... minimal	0	0			0	1
dermis; Inflammation; few	0	0			0	1
.... minimal	0	0			0	1
SPINAL COLUMN						
Examined	5	5			5	5
Normal	5	5			5	5
SPINAL CORD, THORACOLUMBAR						
Examined	5	5			5	5
Normal	5	5			5	5
Hemorrhage; acute, few	0	0			0	0
.... minimal	0	0			0	0
Hemorrhage; acute, focal	0	0			0	0
.... minimal	0	0			0	0
SPLEEN						
Examined	5	5			5	5
Congestion	5	5			5	4
.... mild	4	4			4	2
.... moderate	1	1			1	2
Hematopoiesis	5	5			5	5
.... mild	5	4			3	4
.... moderate	0	1			2	1
.... marked	0	0			0	0

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1		Group 2			
	0 ug/kg IV	88.1 ug/kg IV			0 ug/kg IV	88.1 ug/kg IV
Number of Animals:	5	5			5	5
STOMACH, INCLUDING NONGLANDULAR						
Examined	5	5			5	5
Normal	1	0			0	1
mucosa; glandular; Hemorrhage; acute, few	0	1			0	0
.... minimal	0	1			0	0
non-glandular; epithelium; Hyperplasia; multifocal	0	0			0	0
.... mild	0	0			0	0
glandular; submucosa; Inflammation; diffuse	0	0			0	0
.... mild	0	0			0	0
submucosa; glandular; Inflammation; few	1	2			2	1
.... minimal	1	2			2	1
submucosa; glandular; Inflammation; multifocal	3	3			2	2
.... minimal	1	1			0	0
.... mild	2	2			2	2
submucosa; non-glandular; Inflammation; few	3	2			3	2
.... minimal	3	2			3	2
submucosa; non-glandular; Inflammation; multifocal	0	1			1	0
.... mild	0	1			1	0
non-glandular; epithelium; Hyperkeratosis; multifocal	0	0			0	0
.... mild	0	0			0	0
non-glandular; epithelium; Inclusion; few	0	0			0	0
.... minimal	0	0			0	0
TESTES						
Examined	5	5			.	.
Normal	5	5			.	.
seminiferous tubule; Hemorrhage; acute, few	0	0			.	.
.... minimal	0	0			.	.
THYMUS						
Examined	5	5			5	5
Normal	2	2			2	3
Hemorrhage; acute, few	1	2			1	1
.... minimal	1	2			0	1
.... mild	0	0			1	0

General Footnote: [. Not Applicable]

Table 9 (continued): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
THYMUS (Continued...)						
Hemorrhage; acute, focal	0	0			0	0
.... minimal	0	0			0	0
Hemorrhage; acute, multifocal	2	1			2	1
.... minimal	2	0			2	1
.... mild	0	1			0	0
THYROID GLAND						
Examined	5	5			5	5
Normal	3	2			1	4
Cyst; ultimobranchial, few	1	2			4	0
.... minimal	1	1			2	0
.... mild	0	1			2	0
Cyst; ultimobranchial, focal	1	1			0	1
.... minimal	1	1			0	1
Inflammation; focal	0	1			0	0
.... minimal	0	1			0	0
TRACHEA						
Examined	5	5			5	5
mucosa; Hemorrhage; acute, few	0	2			0	1
.... minimal	0	0			0	0
.... mild	0	2			0	1
mucosa; Hemorrhage; acute, focal	1	1			0	0
.... mild	1	1			0	0
mucosa; Hemorrhage; acute, multifocal	0	0			0	0
.... mild	0	0			0	0
mucosa; Hemorrhage; few	0	0			0	0
.... minimal	0	0			0	0
mucosa; Inflammation; multifocal	5	5			5	5
.... minimal	3	2			0	2
.... mild	2	3			5	3
.... moderate	0	0			0	0
mucosa; glands; Dilation; multifocal	5	5			5	5
.... minimal	1	0			1	0
.... mild	1	2			2	0
.... moderate	1	2			1	3

General Footnote: [. Not Applicable]

Table 9 (concluded): Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice Number of Animals:	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	5	5	5	5		
TRACHEA (Continued...)						
.... marked	2	1			1	2
URINARY BLADDER						
Examined	5	5			4	5
Normal	5	5			4	4
Not Examined: No Section	0	0			1	0
submucosa; Edema; diffuse	0	0			0	1
.... moderate	0	0			0	1
submucosa; Congestion; multifocal	0	0			0	1
.... mild	0	0			0	1
UTERUS						
Examined	.	.			5	5
Normal	.	.			3	4
Dilation	.	.			2	1
.... mild	.	.			0	1
.... moderate	.	.			1	0
.... marked	.	.			1	0
VAGINA						
Examined	.	.			5	5
Normal	.	.			5	5

General Footnote: [. Not Applicable]

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Appendix A

PROTOCOL AND AMENDMENTS



Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

I. SRI STUDY NUMBER	M038-13
II. SPONSOR:	National Institutes of Health National Institute of Mental Health, NIH, DHHS NCS Building, Rm. 7185 (MSC 9641) 6001 Executive Blvd. Bethesda, Maryland 20892-9641
Contract and WA Number:	HHSH271200900018C, WA#16
Sponsor's Representatives:	Jamie Driscoll, Project Officer, NIMH Phone: (301) 443-5288 Fax: (301) 451-5615 Email: jdriscoll@mail.nih.gov
	Robert Innis, Ph.D. NIMH Phone: (203) 401-4309 Fax: (301) 480-3610 Email: Innisr@intra.nih.nih.gov
III. TESTING FACILITY:	SRI International Biosciences Division 333 Ravenswood Avenue Menlo Park, CA 94025
Study Director:	Howard Stock, Ph.D Phone: 650-859-2766 Fax: 650-859-3444 Email: howard.stock@sri.com

IV. PROPOSED IN-LIFE SCHEDULE:

Start of In-Life (first dose):	June 12, 2013
Termination (final necropsy):	June 26, 2013

V. APPROVALS

Jamie Driscoll
 Jamie Driscoll, Sponsor's Representative

6/10/13
 Date

Robert Innis, Sponsor's Representative

 Date

Howard Stock, SRI Study Director

 Date

REVIEWED BY:

SRI Quality Assurance

 Date



Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

I. SRI STUDY NUMBER	M038-13
II. SPONSOR:	National Institutes of Health National Institute of Mental Health, NIH, DHHS NCS Building, Rm. 7185 (MSC 9641) 6001 Executive Blvd. Bethesda, Maryland 20892-9641
Contract and WA Number:	HHSH271200900018C, WA#16
Sponsor's Representatives:	Jamie Driscoll, Project Officer, NIMH Phone: (301) 443-5288 Fax: (301) 451-5615 Email: jdrisco1@mail.nih.gov
	Robert Innis, Ph.D. NIMH Phone: (203) 401-4309 Fax: (301) 480-3610 Email: Innisr@intra.nimh.nih.gov
III. TESTING FACILITY:	SRI International Biosciences Division 333 Ravenswood Avenue Menlo Park, CA 94025
Study Director:	Howard Stock, Ph.D Phone: 650-859-2766 Fax: 650-859-3444 Email: howard.stock@sri.com
IV. PROPOSED IN-LIFE SCHEDULE:	
Start of In-Life (first dose):	June 12, 2013
Termination (final necropsy):	June 26, 2013
<hr/> V. APPROVALS <hr/>	
Jamie Driscoll, Sponsor's Representative	Date
Robert B. Innis, A	Date
Robert Innis, Sponsor's Representative	Date
Howard Stock, SRI Study Director	Date
REVIEWED BY:	
SRI Quality Assurance	Date

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

VI. PURPOSE OF STUDY

The purpose of this study is to provide data of suitable quality and integrity to support applications to the U.S. Food and Drug Administration (FDA) and other regulatory agencies. Therefore, this study will be performed in accordance with the U.S. FDA "Good Laboratory Practice for Nonclinical Laboratory Studies" (GLP) as described in 21 CFR Part 58.

VII. STUDY OBJECTIVE

The Objective of this study is to determine potential toxic effects and to identify potential target organs of toxicity, if possible, for the toxicity endpoints examined following a single intravenous (iv) bolus administration of ER176 given to the Sprague Dawley rats. Additionally, maximum tolerated dose (MTD) and no observable adverse effect level (NOAEL) of ER176 in rats may be established. Information from this study may be used to determine the suitability of the proposed human dose.

VIII. SPONSOR RESPONSIBILITIES

The Sponsor is responsible for the following:

1. Documentation on the strength, purity, composition, physical properties and other pertinent information on the bulk test article in the form of a Certificate or Record of Analysis for inclusion in the final report. SRI will conduct chromatographic purity verification of the test article before and after the test article is used for the study.
2. Providing sufficient quantity of test article.

IX. EXPERIMENTAL DESIGN

Group	Target Dose^{a,*}	µg/m²	µg/kg	Dose Con. (µg/ml)	Dose Volume (ml/kg)^a	# Rats Sacrificed	
						Day 3 Main^{**}	Day 15 Recovery
1	0 (vehicle)	0	0	0	5	5M/5F	5M/5F
2	ER176 100x Human Dose	528.6	88.1	17.6	5	5M/5F	5M/5F
Total # of Rats						10 M/10 F	10 M/10 F

^a The dose volume may be adjusted to achieve the target dose levels based on actual measured concentration of dose solution. Any change will be approved by the Study Director and documented in the study records.

* Maximum human dose of ER176 is 10 µg per 70 kg person. 10 µg/70 kg = 0.143 µg/kg x 37 (human surface area conversion) = 5.286 µg/m². Scaling for the rat gives 5.286 µg/m² / 6 (rat surface area conversion) = 0.881 µg/kg as an equivalent human dose. 100 x 0.881 = 88.1 µg/kg.

** Day 1 is the day of dose administration

Species and Strain: Sprague Dawley rat

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Route of Administration: Intravenous (iv) via tail vein

Frequency: Single dose on Day 1

Dosing Volume: 5 ml/kg; slow bolus. Dose volumes will be calculated based on the animal's most recent body weight. The dose volume may be adjusted to achieve the target dose levels based on actual measured concentration of dose solution.

Duration of In-life Phase: 15 days

X. MATERIALS AND METHODS

A. Test and Control Articles

1. Test Article: ER176

Supplier: PET Chemistry, MIB/NIMH/NIH (Bethesda, MD)

Manufacturer: Dipartimento Scienze Farmaceutiche (Universita di Pisa)

Lot Number: 040711-2

Physical Description: Yellow crystals

Storage Conditions: -25 to -10°C

Characterization of Test Article: Characterization of the test article is the responsibility of the Sponsor. A Certificate of Analysis (CofA), or equivalent documentation, will be provided to SRI for inclusion in the final report. The raw data generated by the Sponsor in support of this CofA or its equivalent will not be verified or maintained by SRI. Test article chromatographic purity will be analyzed by SRI before and after test article is used for study.

2. Vehicle Control: 10% Ethanol/90% Saline

Supplier: To be included in the final report

Manufacturer: To be included in the final report

Lot Number: To be included in the final report

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Physical Description:	Clear, colorless solution
Storage Conditions:	Room temperature
Characterization of Vehicle Control:	Information on the identity, purity, and stability of the control article may be obtained by recording all of the pertinent information provided on the container labels or in a CofA provided by the supplier.
3. Preparation of Dose Formulations:	Dose formulations will be prepared by mixing the appropriate amount of test article in the vehicle to achieve the target concentration, and using a sterile stir bar and/or sonication to mix the formulation.
Storage of Dose Formulations:	Dose formulation(s) will be stored refrigerated at 2-8°C and protected from the light until the day of use. Formulation(s) will be brought to room temperature prior to administration to the animals.
4. Characterization of Dose Formulations:	Assays to verify dose formulation, concentration and homogeneity, and stability under the conditions of the study will be performed by SRI prior to, or concurrently with the study (see Attachment A). Verification of dose formulation concentration will be performed before administration and shall be $\pm 10\%$ of theoretical. If the concentrations of the formulations fall outside $\pm 10\%$ of the theoretical concentration, the Study Director will determine whether adjustments to the dosing volume may be made so that the appropriate dosage of the test article is administered.
5. Test Article Handling:	At a minimum personnel handling the test and control article formulations will wear eye protection, gloves, and a protective smock or laboratory coat.
6. Disposition:	At the end of the study any remaining partially used and unused containers of vehicle control and test article will be shipped to the Sponsor unless the Sponsor issues other directions.

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Residual dose formulations will be discarded after analysis, when the final report is submitted, or when samples no longer afford evaluation.

Empty control and test article containers may be destroyed by SRI on submission of the final report to the Sponsor.

See Section XI.D, "Regulatory Compliance," for information about retention of records and study samples.

7. Method for Assuring Correct Dosing:

The administration of each dose formulation will be properly documented, and the amount administered to each animal will be recorded.

B. Test System

Species:	Rat
Strain:	Sprague Dawley
Supplier:	Charles River or other reputable supplier
Number of Animals:	40 assigned to test;
Sex:	20 males and 20 females
Age at First Dose:	7-9 weeks
Weight Range At First Dose:	235-335 g (males) 150-250 g (females)
Animal Care:	General procedures for animal care and housing will be in accordance with the National Research Council (NRC) <i>Guide for the Care and Use of Laboratory Animals</i> , 8 th edition (2011) and the Animal Welfare Standards incorporated in 9 CFR Part 3, 1991.
Quarantine:	At least 3 days
Housing:	2-3 per cage
Cages:	Hanging polycarbonate cages with hardwood chip bedding

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Light Cycle:	12 hr light/12 hr dark
Temperature:	68–79°F
Humidity:	30–70%. Brief excursions outside this range may occur; excursions of less than 4 hr/day will not be considered deviations from the protocol.
Ventilation:	At least 10 room volumes per hour, with no recirculation of air.
Food:	Harlan Teklad Certified Rodent Chow #2018C or Purina Certified Rodent Chow #5002 or equivalent, <i>ad libitum</i> . Feed is analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed are not present at levels that would affect the study. Documentation of feed analyses is maintained at SRI for reference. A copy of the lot specific reports provided by the supplier will be maintained in the study records.
Water:	Water (purified, reverse osmosis) will be provided <i>ad libitum</i> . Based on previous reports, no contaminants that could interfere with and affect the results of the study are expected to be present in the water. Copies of annual analysis reports are maintained at SRI for reference.

Assignment of Animals to Study

Day:	No more than 3 days before initiation of treatment.
Randomization:	Animals will be randomly assigned to treatment groups via a computerized body weight stratification procedure. Animals may be excluded based on health or inappropriate weight.
Identification:	Animals will be individually identified by a unique ear punch or by another approved method.
Welfare of the Animals:	Every effort will be made to minimize, if not eliminate, pain and suffering in all animals in this study. Moribund animals and animals experiencing undue pain and suffering will be euthanized at the discretion of the Study Director, attending veterinarian, or other qualified person. The Study

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Director will make every effort to protect the scientific validity of the study.

C. Experimental Procedure (In-Life Evaluations)

1. Dose Administration: Intravenous (iv) injection. This route of administration is proposed for clinical use of the test article in humans.

2. Mortality/Morbidity: Animals will be checked at least once daily

3. Clinical Observations: Recorded immediately post dose and approximately 2–4 hr postdose on treatment days and once daily on Days 2–15, or more often as clinical signs warrant, and on the day of necropsy. Animals will be examined for any altered clinical signs, including gross motor and behavioral activity, and observable changes in appearance.

4. Body Weights: Body weights will be recorded on Day 1 (pre-dose) and Day 3 for all animals, and additionally on Day 15 for recovery animals.

Body weights will be recorded for animals found dead and for any euthanized early, but these weights will not be included in the statistical evaluations.

5. Food Consumption: Quantitatively measured for approximately a 24 hr period twice weekly for each cage throughout the study. The total cage consumption per interval will be divided by the number of animals in the cage to determine the average daily food consumption per animal.

6. Clinical Pathology Evaluations:

Preparation of Animals: Animals will **not be fasted** before blood collection.

Method of Collection: Blood will be collected from the retro-orbital sinus of rats under 60% CO₂/40% O₂ anesthesia. Hematology samples will be collected using K₃EDTA as the anticoagulant. No anticoagulant will be used for serum chemistry samples.

Frequency: On Day 3 for animals scheduled for main sacrifice and Day 15 for recovery animals.

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Clinical pathology parameters that will be evaluated are listed below. In some cases automated analyzers report additional parameters not specified in the protocol. Results for the additional parameter(s) will be included in the data package, but will not be summarized, analyzed, or reported, and their collection will not be considered deviations from the protocol.

Hematology Parameters:

- Hematocrit (HCT)
- Hemoglobin (HGB)
- Red blood cell count (RBC)
- Red blood cell distribution width (RDW)
- White blood cell count (WBC)
- WBC differential and absolute counts
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCC)
- Platelet count (PLC)
- Mean platelet volume (MPV)
- Reticulocyte count (absolute, REA, and percent, RET)

Serum Chemistry Parameters:

- Bilirubin, total (TBI)
- Creatinine (CRE)
- Sodium (SOD)
- Potassium (POT)
- Chloride (CHL)
- Cholesterol (CHO)
- Triglycerides (TRI)
- Glucose (GLU)
- Blood urea nitrogen (BUN)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (ALP)
- Calcium (CAL)
- Phosphorus (PHO)
- Protein, total (TPR)
- Albumin (ALB)
- Albumin/globulin ratio (AGR)

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- Globulin (GLO)

D. Necropsy

Interval: Day 3 (main) and Day 15 (recovery) for designated animals. Necropsies will also be performed for any animals found dead or euthanized in moribund condition.

Euthanasia: An overdose of sodium pentobarbital administered by intraperitoneal injection.

Observations: External examination of all body orifices and an examination of all cranial, thoracic, and abdominal organs will be performed, and all gross findings will be recorded.

Tissues Retained: The following tissues will be collected from all animals in the Main Group and the Recovery Group, including those found dead and moribund animals. Tissues will be retained in 10% neutral buffered formalin, except where noted:

- All gross lesions (including tissue masses and abnormal regional lymph nodes)
- Adrenal glands
- Aorta
- Bone (femur with femoro-tibial joint)
- Bone, sternum (marrow histology)
- Bone marrow smear, sternum (for cytology, except for found dead animals)
- Brain (fore-, mid-, and hindbrain)
- Cecum
- Cervix
- Colon
- Duodenum
- Epididymes
- Esophagus
- Eyes, with optic nerve (fixed with formol alcohol preservative)
- Heart
- Identification; (retained in formalin; not processed for histology)
- Ileum
- Injection site(s) tissue. (Entire Tail)
- Jejunum
- Kidneys

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- Liver
- Lungs with bronchi
- Lymph nodes, mandibular and mesenteric
- Mammary gland (when present in regular abdominal skin section, include nipple and surrounding tissue)
- Ovaries
- Pancreas
- Pituitary gland
- Prostate
- Rectum
- Salivary gland, mandibular
- Sciatic nerve
- Seminal vesicle
- Skeletal muscle
- Skin, ventral abdomen, taken with mammary gland
- Spinal cord retained within spinal column (thoracolumbar only)
- Spleen
- Stomach (include nonglandular stomach)
- Testes
- Thymus
- Thyroid/parathyroid glands
- Trachea
- Urinary bladder
- Uterus
- Vagina

**Final Body/
Organ Weights:**

Body weight will be recorded on the day of necropsy for body to organ weight ratios. The following organs will be weighed. Paired organs will be weighed together.

- Adrenal glands
- Brain
- Heart
- Kidneys
- Liver
- Ovaries
- Spleen
- Testes, without epididymes
- Thymus

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Organ weights will be recorded for animals found dead or sacrificed in moribund condition, but these data will not be included in statistical evaluations.

E. Histopathologic Examination:

Tissues: Tissues listed above will be processed and evaluated for the following:

- All animals in the control and high dose groups
- Animals with an unscheduled death or euthanized in moribund condition
- Any tissue identified as a target organ of toxicity by the pathologist (examined in all other dose groups)
- Any other tissue deemed necessary by the pathologist
- All gross lesions will be processed for all animals.
- If neurological clinical signs are not present, only a representative sample of the thoracolumbar (or thoracic) section of the spinal cord will be collected, processed and evaluated. If neurological clinical signs are observed, representative sections of all available spinal cord tissues (cervical, thoracic and lumbar sections) will be collected, processed and evaluated.

Tissue Sections: Sections of the tissues will be embedded in paraffin, cut approximately 5 μm thick, and stained with hematoxylin and eosin by a histology laboratory qualified by SRI.

Evaluated by: A board-certified veterinary pathologist

Method: Each lesion will be listed and coded by the most specific topographic and morphologic diagnoses, severity, and distribution, using Systematized Nomenclature of Medicine (SNOMED) and National Toxicology Program Toxicology Data Management System (TDMS) as guides. A four-step grading system (minimal, mild, moderate, and marked) will be used to define gradable lesions for

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comparison between treated and control groups. Data will be recorded and summarized using Provantis version 8.6.1.3 and/ or Labcat Histopathology version 4.32. Records of gross findings for a specimen from postmortem observations will be available to the pathologist when examining that specimen microscopically.

F. Evaluation of Data:

Parameters:

Mean and standard deviation will be calculated for body weight, food consumption, clinical pathology, and organ weight data at each evaluation interval. Calculations will be performed using Provantis version 8.6.1.3, Labcat Clinical Pathology version 4.42, MS Excel 2003 or 2007, or other appropriate program.

Proposed Statistical Tests:

Body weights, organ weights and clinical pathology data will be evaluated by one-way analysis of variance (ANOVA), followed by Dunnett test (if the ANOVA is significant). All other numeric parameters will be evaluated by Student *t*-test, unless specified otherwise. If appropriate, other post hoc analyses may also be performed. For clinical pathology data, values for parameters that are not within the detection threshold will not be included in the statistical evaluation.

Criteria for Null Hypothesis Rejection: $p \leq 0.05$

G. Control of Bias

While evaluating the responses of the animals and conducting the analyses, the technical staff will be aware of the treatment history of each animal and sample. Based on the relatively objective endpoints to be examined, however, bias is not expected to influence the results of the study.

XI. REGULATORY COMPLIANCE

A. Good Laboratory Practice Compliance

This study is intended to be submitted to and reviewed by the U.S. FDA or an equivalent regulatory agency, and this study therefore will be performed in accordance

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with the U.S. FDA “Good Laboratory Practice for Nonclinical Laboratory Studies,” as described in 21 CFR Part 58, with the following exceptions:

- Various pre-initiation study activities (e.g., receipt and quarantine of animals, pre-initiation body weights and randomization) may be performed prior to the approval of the protocol. These activities will be conducted according to testing facility SOPs, but because they may be conducted before the protocol is signed, they may not be considered by the FDA to have been conducted in compliance with GLP requirements.
- Animal water, bedding, and food analysis will not be performed under GLP compliance by the vendors.

B. Standard Operating Procedures (SOPs)

All operations pertaining to this study, unless specifically defined in this protocol, will be performed according to the SOPs of the laboratory. All deviations from any SOP and the reasons for the deviations will be documented and acknowledged by the Study Director.

C. Protocol Amendments and Deviations

All changes or revisions made to the approved protocol by any involved party and the reasons for the changes and revisions will be documented, signed, and dated by the Study Director and the Sponsor’s Representative. Amendments will be maintained with the protocol. Verbal or email approval for changes in the protocol may be granted by the Sponsor’s Representative, but a written amendment as described above will follow.

All deviations from the protocol and the reasons for the deviations will be documented and acknowledged by the Study Director. The Sponsor’s Representative will be informed of the occurrence of any deviations that might affect the results of the study, and any corrective actions taken.

D. Retention of Records and Study Samples

The original protocol, amendments, final report, raw data, supporting documents, and records as well as all pathology materials (slides, blocks, and wet tissue specimens) specific to this study will be retained and stored by SRI International. All records and materials will be maintained for a period of at least 1 year. At the end of the retention period, the Sponsor will be contacted for instructions regarding disposition of these materials.

XII. REPORTING

The final report will accurately and completely describe the study design, procedures, and findings. An analysis and summary of the data followed by the

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conclusions derived from the analyses will also be included. A draft report will be issued prior to submission of the final report.

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Attachment A

ANALYTICAL CHEMISTRY:

**DOSE VERIFICATION, HOMOGENEITY, STABILITY ANALYSES, AND TEST
ARTICLE CHROMATOGRAPHIC PURITY**

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
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XIII. INTRODUCTION

Dose verification analyses will be performed on formulations containing the test article, ER176, in the selected vehicle, 10% Ethanol/ 90% Saline. Concentration, homogeneity, and stability of test article in the vehicle will be determined by high performance liquid chromatography (HPLC). In addition, test article chromatographic purity will be analyzed using the same HPLC method. The methodology, procedures, and final results will be documented in the Final Report.

XIV. EXPERIMENTAL

A. Reference Standard

The test article, ER176, will be used as the reference standard in the analyses.

B. Analytical Method

Instrument: Hewlett-Packard Model 1100 series liquid chromatography system

Column: Phenomenex Luna C18 (2), 250 x 4.6 mm, 10 μ m or equivalent

Mobile Phases: Methanol: water 72:28, v/v

Run Time: 12 min

Diluent: Vehicle (10% Ethanol/90% Saline)

Flow Rate: 2.5 ml/min

Injection Volume: 10 μ l or as needed

Detection: UV wavelength at 235 nm

Column Temp.: 25°C

Data System: HP Chemstation Software

Note: An equivalent column or instrument may be used. Minor adjustments in the method e.g., amounts of the mobile phase ingredients or injection volume, may be made by the analyst, only if necessary, to achieve desired chromatographic characteristics.

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C. Preparation of Solutions and Samples

1. Preparation of Standard Solutions

Standard Stock Solution: A sample of the test article standard will be weighed and dissolved in Ethanol (10% of the final volume), then Saline (90% of the final volume) will be added and mixed to assure complete dissolution of the ER176 in the equivalent of the diluent, 10% Ethanol: 90% Saline, to make standard stock solution (Sa). To ensure the accuracy of the standard stock solution, a second standard stock solution (Sb) will be prepared in the same way as Sa.

Calibration Standard Solutions: For each experiment, a minimum of five standard solutions at different concentrations will be prepared from the stock solution using the diluent. The calibration solutions will be chromatographed to demonstrate the linearity of the calibration curve over the concentration range of interest.

2. Preparation of Formulation Samples

For dose verification, a minimum of duplicate aliquots will be sampled for each concentration.

For homogeneity testing, triplicate aliquots will be sampled from the lowest and the highest concentration of formulations. Aliquots will be taken from the top, middle, and bottom of a fully mixed formulation to demonstrate homogeneity.

For stability determination, a minimum of duplicate aliquots will be sampled and analyzed. Stability will be established over a concentration range that covers the dose levels used in the study.

For Chromatographic purity, a stock standard solution (Sa) or (Sb) will be analyzed.

Aliquots will be accurately transferred into separate volumetric flasks or selected container and diluted to the desired concentration with the diluent. Formulations may be transferred directly to an HPLC vial if the concentration is within the range of the calibration curve.

D. Analysis

1. System Suitability

A single standard solution will be chromatographed six consecutive times to determine the system repeatability (reported as relative standard deviation, % RSD, of peak area or response factor). The % RSD should be $\leq 3.0\%$ for the six injections.

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The response factors of the calibration standards and the standards used during the run (e.g., bracketing standards) will be calculated. The % RSD of these response factors should be $\leq 10.0\%$.

The response factor of the accuracy check standard Sb will be compared to the response factor of the standard stock solution Sa. The accuracy of the two corresponding solutions (Sa vs. Sb) when compared should be within $100.0 \pm 5.0\%$.

2. Linearity

Each of the calibration standards will be chromatographed, and a linear regression calibration curve will be generated. The correlation coefficient (r) should be ≥ 0.990 .

3. Dose Verification

At a minimum, duplicate samples from each dose level will be analyzed. The verified concentration, reported as a percentage of the nominal concentration, will be averaged and the averaged value should be within $100.0 \pm 10.0\%$ of the nominal concentration.

4. Homogeneity

Triplicate samples (top, middle, and bottom) from each of the lowest and highest concentrations of formulation will be analyzed. The individual values, reported as percentages of nominal concentration, from each set of triplicate samples will be averaged and the % RSD for each set should be $\leq 5.0\%$. Homogeneity analysis needs to be determined only once for the study.

5. Stability Determination

Stability of formulations over a concentration range bracketing those used in the study will be established prior to, or concurrently with the study. Formulations will be stored under the conditions that the study required for stability evaluation. Stability results should be within $100.0 \pm 10.0\%$ of the initial concentrations. In the case that stability is established concurrently with the study, stability results will also be evaluated against the nominal concentrations. Stability determination will be established only once for the study under the given concentration range and set of storage conditions.

6. Test Article Chromatographic Purity

SRI will perform chromatographic purity analyses for the test article once on the first analytical testing day and once on or after the last dose preparation to bracket the period of test article use. The same HPLC method will be used for both chromatographic purity and formulation concentration analysis. The results,

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when compared, should be within $100.0 \pm 10.0\%$. The results will be used to evaluate the test article stability during the study period.

E. Calculations

Concentration of test article in the vehicle will be determined by HPLC using an external standard method. The linear regression curve obtained from the calibration standards will be used to calculate the concentration of the test article in each dose formulation. Results from each concentration level will be averaged as a percentage of the nominal concentration. Homogeneity will be measured as % RSD of the triplicate samplings at the lowest and highest concentration levels. Stability results will be calculated using the linear regression curves and averages reported as percent of the initial concentration. Chromatographic purity will be calculated with normalized peak area percentage.

III. RESULTS/DISCUSSION

Experimental results will be discussed and compared to the criteria in the Study Protocol. Deviations from the criteria will be documented and reported to the Study Director. Analytical methods, procedures, and raw data will be archived with the study records, and an analytical summary report will be included as an appendix to the final report.



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PROTOCOL TITLE:

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

SRI Study Number:

M038-13

Sponsor:

National Institutes of Health, National Institute of Mental Health, NIH, DHHS

Sponsor's Representatives:

Jamie Driscoll, Project Officer, NIMH
Phone: (301) 443-5288 Fax: (301) 451-5615
Email: jdrisco1@mail.nih.govRobert Innis, Ph.D. NIMH
Phone: (203) 401-4309 Fax: (301) 480-3610
Email: Innisi@intra.nimh.nih.gov

SRI Study Director:

Howard Stock, Ph.D

This amendment modifies the following lines/sections of the study protocol. Additions are in bold and italics: ***addition***. Deleted text has been struck through: ~~deleted~~.

IX. EXPERIMENTAL DESIGN

Group	Target Dose ^{a,*}	$\mu\text{g}/\text{m}^2$	$\mu\text{g}/\text{kg}$	Dose Con. ($\mu\text{g}/\text{ml}$)	Dose Volume (ml/kg) ^a	# Rats Sacrificed	
						Day 3 Main ^{**}	Day 15 Recovery
1	0 (vehicle)	0	0	0	5	5M/5F	5M/5F
2 [*]	ER176 100x Human Dose	528.6	88.1	17.6	5	5M/5F	5M/5F
3 ^b	<i>ER176</i> <i>25x Human Dose</i>	<i>132.5</i>	<i>22.0</i>	<i>4.4</i>	<i>5</i>	<i>10M/10F</i>	<i>N/A</i>
4 ^c	<i>ER176</i> <i>50x Human Dose</i>	<i>264.3</i>	<i>44.1</i>	<i>8.8</i>	<i>5</i>	<i>10M/10F</i>	<i>N/A</i>
5 [*]	<i>ER176</i> <i>100x Human Dose</i>	<i>528.6</i>	<i>88.1</i>	<i>17.6</i>	<i>5</i>	<i>10M/10F</i>	<i>N/A</i>
	Total # of Rats					410 M/410 F	10 M/10 F

^a The dose volume may be adjusted to achieve the target dose levels based on actual measured concentration of dose solution. Any change will be approved by the Study Director and documented in the study records.

* Maximum human dose of ER176 is 10 μg per 70 kg person. $10 \mu\text{g}/70 \text{ kg} = 0.143 \mu\text{g}/\text{kg} \times 37$ (human surface area conversion) = 5.286 $\mu\text{g}/\text{m}^2$. Scaling for the rat gives $5.286 \mu\text{g}/\text{m}^2 / 6$ (rat surface area conversion) = 0.881 $\mu\text{g}/\text{kg}$ as an equivalent human dose. $100 \times 0.881 = 88.1 \mu\text{g}/\text{kg}$.

^b Maximum human dose of ER176 is 10 μg per 70 kg person. $10 \mu\text{g}/70 \text{ kg} = 0.143 \mu\text{g}/\text{kg} \times 37$ (human surface area conversion) = 5.286 $\mu\text{g}/\text{m}^2$. Scaling for the rat gives $5.286 \mu\text{g}/\text{m}^2 / 6$ (rat surface area conversion) = 0.881 $\mu\text{g}/\text{kg}$ as an equivalent human dose. $25 \times 0.881 = 22.0 \mu\text{g}/\text{kg}$. $5.286 \mu\text{g}/\text{m}^2 \times 0.25 = 132.5 \mu\text{g}/\text{m}^2$

^c Maximum human dose of ER176 is 10 μg per 70 kg person. $10 \mu\text{g}/70 \text{ kg} = 0.143 \mu\text{g}/\text{kg} \times 37$ (human surface area conversion) = 5.286 $\mu\text{g}/\text{m}^2$. Scaling for the rat gives $5.286 \mu\text{g}/\text{m}^2 / 6$ (rat surface area conversion) = 0.881 $\mu\text{g}/\text{kg}$ as an equivalent human dose. $50 \times 0.881 = 44.1 \mu\text{g}/\text{kg}$. $5.286 \mu\text{g}/\text{m}^2 \times 0.50 = 264.3 \mu\text{g}/\text{m}^2$

** Day 1 is the day of dose administration



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X. MATERIALS AND METHODS

B. Test System

Number of Animals: **100** 40 assigned to test;

Sex: **50** 20 males and **50** 20 females

C. Experimental Procedure (In-Life Evaluations)

3. Clinical Observations:

Recorded immediately post dose and approximately 2–4 hr postdose on treatment days and once daily on Days 2-15, or more often as clinical signs warrant, and on the day of necropsy. Animals will be examined for any altered clinical signs, including gross motor and behavioral activity, and observable changes in appearance.

For Groups 3-5: Recorded immediately post dose and approximately 15, 30, 60, 90, and 120 minutes post dose on treatment day and once daily on Day 2, or more often as clinical signs warrant, and on the day of necropsy.

4. Food Consumption:

Quantitatively measured for approximately a 24 hr period twice weekly for each cage throughout the study. The total cage consumption per interval will be divided by the number of animals in the cage to determine the average daily food consumption per animal.

For Groups 3-5: Food consumption will not be measured.

6. Clinical Pathology Evaluations:

Frequency:

On Day 3 for animals scheduled for main sacrifice and Day 15 for recovery animals.

For Groups 3-5: Clinical pathology will not be measured.

D. Necropsy

Interval:

Day 3 (main) and Day 15 (recovery) for designated animals. Necropsies will also be performed for any



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animals found dead or euthanized in moribund condition.

For Groups 3-5: Day 3. Gross necropsies and histopathology will not be performed.

Reason for Change:

Due to clinical observations (ataxia and hyperactivity) observed in the drug treated animals (Group 2) immediately post-dose, Groups 3-5 have been added to better examine the clinical observations at lower doses.

Effect on the Study:

The inclusion of these lower dose groups (Groups 3-5) will help us better understand the dose relationship between ER176 and the clinical observations.

Effective Date:

Date of Study Director's Signature

APPROVALS

See Email Approval

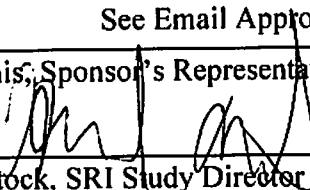
Jamie Driscoll, Sponsor's Representative

Date

See Email Approval

Robert Innis, Sponsor's Representative

Date


Howard Stock, SRI Study Director

Date

17 Oct 2013

Minh Bui

From: Driscoll, Jamie (NIH/NIMH) [E] <jdrisco1@mail.nih.gov>
Sent: Thursday, October 17, 2013 5:40 AM
To: Innis, Robert (NIH/NIMH) [E]; Minh Bui
Cc: Hanna Ng; Howard Stock
Subject: RE: M038-13 Protocol Amendment 1

Minh - I concur, please proceed.

Jamie

-----Original Message-----

From: Innis, Robert (NIH/NIMH) [E]
Sent: Friday, October 11, 2013 5:45 PM
To: Minh Bui; Driscoll, Jamie (NIH/NIMH) [E]
Cc: Hanna Ng; Howard Stock
Subject: RE: M038-13 Protocol Amendment 1

Yes, please proceed.

Thanks

Robert Innis

-----Original Message-----

From: Minh Bui [\[mailto:minh.bui@sri.com\]](mailto:minh.bui@sri.com)
Sent: Friday, October 11, 2013 1:43 PM
To: Driscoll, Jamie (NIH/NIMH) [E]; Innis, Robert (NIH/NIMH) [E]
Cc: Hanna Ng; Howard Stock
Subject: M038-13 Protocol Amendment 1

Hello Dr. Innis and Ms. Driscoll,

Attached is the M038-13 protocol amendment 1, ready for your review and approval. This amendment will add 3 dosing groups (25x, 50x, and 100x) to better examine the clinical observations at lower doses. We currently have the animals scheduled to arrive Thursday 10/17 and this phase of the study to start on Tuesday 10/22. We understand that with the government shutdown, you may not be able to get back to us with your approval in a timely manner so we plan to implement M038-13 protocol amendment 1 if we do not hear back from you by 10/18 unless instructed to do otherwise. If you have any questions or concerns, please do not hesitate to contact us. Thank you.

Minh Bui
Project Manager
SRI International, PN 343
333 Ravenswood Avenue
Menlo Park, CA 94025
Fax # 650-859-6155

Minh Bui

From: Innis, Robert (NIH/NIMH) [E] <innisr@mail.nih.gov>
Sent: Friday, October 11, 2013 2:45 PM
To: Minh Bui; Driscoll, Jamie (NIH/NIMH) [E]
Cc: Hanna Ng; Howard Stock
Subject: RE: M038-13 Protocol Amendment 1

Follow Up Flag: Follow up
Flag Status: Flagged

Yes, please proceed.

Thanks

Robert Innis

-----Original Message-----

From: Minh Bui <mailto:minh.bui@sri.com>
Sent: Friday, October 11, 2013 1:43 PM
To: Driscoll, Jamie (NIH/NIMH) [E]; Innis, Robert (NIH/NIMH) [E]
Cc: Hanna Ng; Howard Stock
Subject: M038-13 Protocol Amendment 1

Hello Dr. Innis and Ms. Driscoll,

Attached is the M038-13 protocol amendment 1, ready for your review and approval. This amendment will add 3 dosing groups (25x, 50x, and 100x) to better examine the clinical observations at lower doses. We currently have the animals scheduled to arrive Thursday 10/17 and this phase of the study to start on Tuesday 10/22. We understand that with the government shutdown, you may not be able to get back to us with your approval in a timely manner so we plan to implement M038-13 protocol amendment 1 if we do not hear back from you by 10/18 unless instructed to do otherwise. If you have any questions or concerns, please do not hesitate to contact us. Thank you.

Minh Bui
Project Manager
SRI International, PN 343
333 Ravenswood Avenue
Menlo Park, CA 94025
Fax # 650-859-6155
Work # 650-859-3289



Protocol Amendment No. 2

PROTOCOL TITLE:

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

SRI Study Number:

M038-13

Sponsor:

National Institutes of Health, National Institute of Mental Health, NIH, DHHS

Sponsor's Representatives:

Jamie Driscoll, Project Officer, NIMH
Phone: (301) 443-5288 Fax: (301) 451-5615
Email: jdrisco1@mail.nih.govRobert Innis, Ph.D. NIMH
Phone: (203) 401-4309 Fax: (301) 480-3610
Email: Innisi@intra.nimh.nih.gov

SRI Study Director:

Howard Stock, Ph.D

This amendment modifies the following lines/sections of the study protocol. Additions are in bold and italics: ***addition***. Deleted text has been struck through: ~~deleted~~.

IX. EXPERIMENTAL DESIGN

Group	Target Dose ^{a,*}	$\mu\text{g}/\text{m}^2$	$\mu\text{g}/\text{kg}$	Dose Con. ($\mu\text{g}/\text{ml}$)	Dose Volume (ml/kg) ^a	# Rats Sacrificed	
						Day 3 Main ^{**}	Day 15 Recovery
1	0 (vehicle)	0	0	0	5	5M/5F	5M/5F
2 [*]	ER176 100x Human Dose	528.6	88.1	17.6	5	5M/5F	5M/5F
3 ^b	ER176 25x Human Dose	132.5	22.0	4.4	5	10M/10F	N/A
4 ^c	ER176 50x Human Dose	264.3	44.1	8.8	5	10M/10F	N/A
5 [*]	ER176 100x Human Dose	528.6	88.1	17.6	5	10M/10F	N/A
	Total # of Rats					40 M/10 F	10 M/10 F

^a The dose volume may be adjusted to achieve the target dose levels based on actual measured concentration of dose solution. Any change will be approved by the Study Director and documented in the study records.

* Maximum human dose of ER176 is 10 μg per 70 kg person. $10 \mu\text{g}/70 \text{ kg} = 0.143 \mu\text{g}/\text{kg} \times 37$ (human surface area conversion) = 5.286 $\mu\text{g}/\text{m}^2$. Scaling for the rat gives $5.286 \mu\text{g}/\text{m}^2 / 6$ (rat surface area conversion) = 0.881 $\mu\text{g}/\text{kg}$ as an equivalent human dose. $100 \times 0.881 = 88.1 \mu\text{g}/\text{kg}$.

^b Maximum human dose of ER176 is 10 μg per 70 kg person. $10 \mu\text{g}/70 \text{ kg} = 0.143 \mu\text{g}/\text{kg} \times 37$ (human surface area conversion) = 5.286 $\mu\text{g}/\text{m}^2$. Scaling for the rat gives $5.286 \mu\text{g}/\text{m}^2 / 6$ (rat surface area conversion) = 0.881 $\mu\text{g}/\text{kg}$ as an equivalent human dose. $25 \times 0.881 = 22.0 \mu\text{g}/\text{kg}$. **Surface area conversion:** $5.286 \mu\text{g}/\text{m}^2 \times 0.25 = 132.5 \mu\text{g}/\text{m}^2$

^c Maximum human dose of ER176 is 10 μg per 70 kg person. $10 \mu\text{g}/70 \text{ kg} = 0.143 \mu\text{g}/\text{kg} \times 37$ (human surface area conversion) = 5.286 $\mu\text{g}/\text{m}^2$. Scaling for the rat gives $5.286 \mu\text{g}/\text{m}^2 / 6$ (rat surface area conversion) = 0.881 $\mu\text{g}/\text{kg}$ as an equivalent human dose. $50 \times 0.881 = 44.1 \mu\text{g}/\text{kg}$. **Surface area conversion:** $5.286 \mu\text{g}/\text{m}^2 \times 0.50 = 264.3 \mu\text{g}/\text{m}^2$

** Day 1 is the day of dose administration



Protocol Amendment No. 2

Reason for Change:

To correct typo in surface area conversion mathematical calculations and add text to clarify surface area conversion.

Effect on the Study:

No impact on study. The appropriate concentrations of ER176 were dosed and assessed.

Effective Date:

Date of Study Director's Signature

APPROVALS

Jamie Driscoll, Sponsor's Representative

Robert B.

Date

Digitally signed by Robert B. Innis
A
On c:\US\cm\US_Government
On 09/05/2013 10:11:00
09:234534000000 100.11 1:00 107
38976, cm=Robert B. Innis - A
Date: 2013-11-06 07:39:07 -0500

Robert Innis, Sponsor's Representative

Innis -A

Date

Howard Stock, SRI Study Director

Date



Protocol Amendment No. 2

Reason for Change: To correct typo in surface area conversion mathematical calculations and add text to clarify surface area conversion.

Effect on the Study: No impact on study. The appropriate concentrations of ER176 were dosed and assessed.

Effective Date: Date of Study Director's Signature

APPROVALS

Jamie Driscoll

Jamie Driscoll, Sponsor's Representative

11/6/13

Date

Robert Linnis

Robert Linnis, Sponsor's Representative

Date

20 Nov 2013

Howard Stock

Howard Stock, SRI Study Director

Date

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Appendix B

ANALYTICAL CHEMISTRY

**Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13**

Appendix B-1

CERTIFICATES OF ANALYSIS

Certificate of Analysis

Generic name	ER176
Chemical name	(R)-N-sec-butyl-4-(2-chlorophenyl)-N-methylquinazoline-2-carboxamide
Structure	
Manufacturer	Dipartimento Scienze Farmaceutiche Università di Pisa Via Bonanno 6, 56126 Pisa Italy
NIMH receiving date	7/2/2012
NIMH lot number	040711-2
Purity	98% by HPLC at 215 nm, >99% by HPLC at 235nm
Expiration date	NA
Storage conditions	Store at controlled room temperature and humidity, protect from light May be stored below 0 °C for long-term storage
Analyses	1. 1H-NMR by Manufacturer 2. 13C-NMR by Manufacturer 3. HPLC by Manufacturer, 3/9/2012 4. LC-MS by NIMH, 9/5/2012 5. HPLC by NIMH, 8/21/2012
Contact	Cheryl Morse, Molecular Imaging Branch, National Institute of Mental Health, 10 Center Drive, Room B3C346, Bethesda MD 20892-1003
Date	5/13/2013

Note: ER176 is a non-hazardous, non-infectious synthetic compound. No MSDS for this compound is available, but the MSDS for the structurally similar PK11195 is enclosed.

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PHARMCO-AAPER

THE POWER OF THREE³

Page 1 of 1

Certificate of Analysis

ETHYL ALCOHOL 200 PROOF, ABSOLUTE

ACS/USP GRADE

LOT # SK1984

QC # C1303192

Date of Manufacture: 03/21/13

Recommended Retest Date: Three Years from Date of Manufacture*

Main Catalog #: 111000200

This product meets or exceeds all specifications as set forth in the current ACS/USP monographs.

TEST	Monograph	SPECIFICATION	Results	
Assay (by GC, corrected for water)	ACS	NLT 99.5%	99.99%	
Assay (by specific gravity@15.56°C)	USP	NLT 99.5%	99.99%	
Water (wt%)	ACS	NMT 0.2%	0.01%	
Proof	27CFR 30.23	Lot Analysis	200.0	
Identification A - Specific Gravity	USP	Not more than 0.7962 @ 15.56°C	0.7937	
Identification Test B	USP	Conforms to Infrared Spectra	Pass	
Color (APHA)	ACS	NMT 10	1	
Clarity of Solution	USP	Sample Solution A & B show same clarity as that of water, or their opalescence is not more pronounced than that of Reference suspension A	Pass	
Color of Solution	USP	The Sample Solution has the appearance of water or is not more intensely colored than the Standard solution	Pass	
Solubility in Water	ACS	To Pass Test	Pass	
Residue on Evaporation	ACS	NMT 0.001%	<0.001%	
Limit of Nonvolatile Residue	USP	The weight of the residue does not exceed 2.5mg	0.1mg	
Acetone/Isopropyl Alcohol	ACS	To Pass Tests	Pass	
Titratable Acid	ACS	NMT 0.0005 meq/g	<0.0002 meq/g	
Titratable Base	ACS	NMT 0.0002 meq/g	0.0001 meq/g	
Acidity or Alkalinity	USP	The solution is pink (30ppm, expressed as acetic acid)	Pass	
Methanol	ACS	NMT 0.1%	<0.1%	
Substances Darkened by Sulfuric Acid	ACS	To Pass Test	Pass	
Substances Reducing Permanganate	ACS	To Pass Test	Pass	
Ultraviolet Absorbance	USP	NMT 0.40 at 240 nm NMT 0.30 between 250 nm and 260 nm NMT 0.10 between 270 nm and 340 nm Absorption curve between 235nm - 340nm is smooth	0.28 0.11 0.01 Pass	
Volatile Impurities	USP	Methanol Sum of Acetal and Acetaldehyde Benzene Total of all other impurities	NMT 200 ppm NMT 10ppm NMT 2ppm NMT 300ppm	None Detected None Detected None Detected None Detected

Form Ethanol, Pure, 200, ACS/USP, #101, Rev 4 7, 01/13, JRW

Approved by: A. Heffernan, Quality Control Chemist

Disclaimer: For Industrial, Pharmaceutical, Flavor & Fragrance or Lab Use. Not intended for use as an active substance in Food or Drug. Not to be considered a Medical Device. Not intended for use as a Disinfectant as defined by the EPA. The appropriate use of this product is the sole responsibility of the user. *Excluding UV/Vis for pure Ethyl Alcohol (See shelf life statement). (Rev. # disclaimer only, rev 3.5 11/06 EF)

Pharmco Products Inc: 58 Vale Road, Brookfield, CT 06804

1.800.243.5360 Fax: 1.203.740.3461

Aaper Alcohol & Chemical Co: 1101 Shelby Drive, Shelbyville, KY 40065

1.800.456.1017 www.pharmcoaaper.com

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Initials: TC Date: 06/17/13



**MEDICATION DELIVERY
NORTH COVE FACILITY**
Hwy 231 N PO Box 1390
Marion N.C. 28752
Telephone: (828) 756-4151
Fax: (828) 756-4821

Certificate of Analysis

Product: 0.9% Sodium Chloride Injection, USP

Lot #: C879213 / C879211JA

Code: 2B1324X

Manufacture/
Sterilization Date: 08/28/2012

Expiry: 02/2014

Chemical Testing per Specification: 03-15-19-061 Issue Date: 10/3/2008

TEST	LIMIT	RESULT
NaCl (g/L)	8.55 - 9.45 g/L	8.80 g/L
Sodium ID	Positive	Positive
Sodium ID- Flame	Positive	Positive
pH at 23 deg. C	4.5 - 7.0	5.7
Particle Analysis	NMT 25 \geq 10 um/vol	NMT 25
Particle Analysis	NMT 3 \geq 25 um/vol	NMT 3
Sterility	Pass Permeable Release	Pass

Lumetus Testing per 13-01-V

RESULT	LIMIT	DISPOSITION	DATE PASSED
< 0.25 EU/ml	< 0.25 EU/ml	Pass	8/30/2012

This is to certify that this product was manufactured according to current GMP and fulfills the requirements of the Master Production Document.

Data Batch Released	Parametric Release Date	Quantity Released
8/30/2012	8/30/2012	24563

Print Name	Signature/Date
Prepared by: <i>Shemie Hudson</i>	<i>Shemie Hudson 8/31/12</i>
Approved by: <i>S. M. Hudson</i> Quality Manager or Designee	<i>S. M. Hudson 8/31/12</i>

Page 1 of 1

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Initials: TC Date: 06/17/13



**MEDICATION DELIVERY
NORTH COVE FACILITY**
Hwy 221 N PO Box 1390
Marion N.C. 28752
Telephone: (828) 756-4151
Fax: (828) 756-4821

Certificate of Analysis

Product: 0.9% Sodium Chloride Injection, USP

Lot #: C901504 / C901504A

Code: 2B1324X

**Manufacture/
Sterilization Date:** 04/16/2013

Expiry: 10/2014

Chemical Testing per Specification: 03-15-19-061 Issue Date: 10/3/2008

TEST	LIMIT	RESULT
NaCl (g/L)	8.55 - 9.45 g/L	8.91 g/L
Sodium ID	Positive	Positive
Sodium ID- Flame	Positive	Positive
pH at 25 deg. C	4.5 - 7.0	5.6
Particle Analysis	NMT 25 \geq 10 $\mu\text{m}/\text{ml}$	NMT 25
Particle Analysis	NMT 3 \geq 25 $\mu\text{m}/\text{ml}$	NMT 3
Sterility	Pass Parametric Release	Pass

Limulus Testing per 13-01-V

RESULT	LIMIT	DISPOSITION	DATE PASSED
< 0.25 EU/ml	< 0.25 EU/ml	Pass	4/18/2013

This is to certify that this product was manufactured according to current GMP and fulfills the requirements of the Master Production Document.

Date Batch Released	Parametric Release Date	Quantity Released
4/18/2013	4/18/2013	NA

Prepared by:	Print Name	Signature/Date
Sherrie Hopson	Sherrie Hopson	4/19/13
Susan Shaw	Susan Shaw	4/19/13

Page 1 of 1

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Original located: Chemical Receipt Binder
Initials: LN Date: 11/7/13

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Appendix B-2

ANALYTICAL CHEMISTRY:

**DOSE VERIFICATION, HOMOGENEITY, STABILITY ANALYSES, AND TEST
ARTICLE CHROMATOGRAPHIC PURITY**

Written by:


Honghui Zhou, BS
Chemist

2/7/14
Date

Approved by:


Joan-Huey Dow, PhD
Manager, Analytical Chemistry

02/10/14
Date

Analytical Chemistry Department
Biosciences Division
SRI International

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

I. INTRODUCTION

Dose verification analyses were performed on formulations containing the test article, ER176, in the selected vehicle, 10% ethanol/90% saline. Concentration, homogeneity, and stability of the test article in the vehicle were determined by high performance liquid chromatography (HPLC). In addition, test article chromatographic purity was analyzed using the same HPLC method. The methodology, procedures, and final results are summarized in this report.

II. EXPERIMENTAL

A. Reference Standard

The test article ER176 (Lot No: 040711-2) was used as the reference standard in the analyses.

B. Analytical Method

Instrument: Hewlett-Packard Model 1100 series liquid chromatography system

Column: Phenomenex Luna C18 (2), 250 x 4.6 mm, 10 μ m

Mobile Phase: Methanol:water 72:28, v/v

Run Time: 12 min

Diluent: Vehicle (10% ethanol/90% saline)

Flow Rate: 2.5 ml/min

Injection Volume: 10 μ l

Detection: UV wavelength at 235 nm

Column Temp.: 25°C

Data System: HP Chemstation Software; version A 08.03

C. Procedures

1. Preparation of Standard Solutions

Standard Stock Solutions: A sample of the test article standard was weighed and dissolved in ethanol (10% of the final volume), then saline (90% of

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

the final volume) was added and mixed to assure complete dissolution of the ER176 in the equivalent of the diluent, 10% ethanol/90% saline, to make standard stock solution (Sa). To ensure the accuracy of the standard stock solution, a second standard stock solution (Sb) was prepared in the same way as Sa. Both Sa and Sb were injected for accuracy checking. Concentrations of the standard stock solutions were ~80 to 106 µg/ml.

Calibration Standard Solutions: With each experiment, six calibration standard solutions at different concentrations were prepared from the stock solution using the diluent. Concentrations of the calibration standards were between ~2 and 88 µg/ml. The calibration standards were chromatographed to demonstrate the linearity of the calibration curve over the concentration range.

For test article purity evaluation, standard solutions of ~80 and 88 µg/ml were prepared and analyzed.

2. Preparation of Sample Solution from Dose Formulation

For dose verification, a minimum of two aliquots were sampled for each dose concentration. Aliquots were transferred directly to an HPLC vial because the concentrations were within the range of the calibration curve.

For homogeneity testing, triplicate aliquots were sampled from the lowest and the highest concentration of formulations. Aliquots were taken from the top, middle, and bottom of a fully mixed solution to demonstrate homogeneity.

For stability determination, two or three aliquots were sampled and prepared.

For chromatography purity evaluation, one of the stock standard solutions on the first analytical testing day and one on the dose formulation preparation day were chosen and analyzed.

D. Analysis

1. System Suitability

A single standard solution was chromatographed six consecutive times to determine the system repeatability (reported as relative standard deviation, % RSD, of peak area or response factor). The % RSD should be $\leq 3.0\%$ for the six injections.

The response factors of the calibration standards and the standards used during the run (e.g., bracketing standards) were calculated. The % RSD of these response factors should be $\leq 10.0\%$.

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

The response factor of Sb was compared to the response factor of the Sa. The percent accuracy of the two, when compared, should be within $100.0 \pm 5.0\%$.

System suitability tests were completed for each experiment for the study. The experiments for the study are referred to as follows:

- Stability T = 0 of mock formulations (12 and 40 $\mu\text{g}/\text{ml}$) on 6/3/13
- Stability T = 3 days refrigerated +1 day room temperature on 6/7/13
- Dose verification/homogeneity of dose formulation on 6/10/13
- Stability T = 0 of mock formulations (4 $\mu\text{g}/\text{ml}$) on 10/4/13
- Stability T = 3 days refrigerated +1 day room temperature on 10/8/13
- Dose verification/homogeneity of dose formulation on 10/21/13

2. Linearity

Each of the calibration standards was chromatographed, and a linear regression calibration curve was generated. The correlation coefficient (r) should be ≥ 0.990 .

3. Dose Verification

Two to three samples from each dose level were analyzed. The verified concentrations, reported as a percentage of the nominal concentration, should be averaged and the averaged value should be within $100.0 \pm 10.0\%$ of the nominal concentration.

4. Homogeneity Determination

Triplicate samples of the formulations were analyzed. Aliquots were taken from the top, middle, and bottom of a fully mixed solution to demonstrate homogeneity. The individual values, reported as percentages of nominal from each set of triplicate samples, were averaged; the % RSD for each set should be $\leq 5.0\%$.

5. Stability Determination

Formulation stability was established prior to the study. Stability results should be within $100.0 \pm 10.0\%$ of the initial concentration.

6. Test Article Chromatographic Purity

Chromatographic purity of the test article was assessed once on the first testing day (i.e., mock formulation stability T = 0 on 6/3/13) and twice on the dose formulation preparation days (6/10/13 and 10/21/13). The same HPLC method was used to assess the dose concentration and chromatographic purity. The purity is calculated by peak area percentage. The results were used to evaluate the test

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

article stability during the study period. The results, when compared, should be within $100.0 \pm 10.0\%$.

E. Calculations

Concentration of the test article in the dose formulations was determined by HPLC using an external standard method. The linear regression curve obtained from the calibration standards was used to calculate the concentration of test article in each formulation. Results from each dose concentration level were averaged as a percentage of the nominal concentration. Homogeneity was measured as % RSD of the triplicate samplings at the lowest and highest concentration levels. Stability results were calculated using the linear regression curve and averages reported as percent of the initial concentration. Chromatographic purity was calculated by normalized peak area percentage.

III. RESULTS/DISCUSSION

A. System Suitability

System suitability results are summarized in Table B-1 for each analytical experiment for the study. All system suitability test results were within the protocol requirements.

The prepared calibration standard curves were also found to be linear, and the correlation coefficients (r) are included in Table B-1. An example of a calibration curve is shown in Figure B-1. Representative HPLC chromatograms of the test article standard solution and formulation sample are shown in Figure B-2.

B. Dose Verification

The dose formulations at nominal concentration range of 4.4 to 17.6 $\mu\text{g}/\text{ml}$ and mock formulations at nominal concentration range of 4 to 40 $\mu\text{g}/\text{ml}$ were tested. Concentrations of the test article in the formulations are shown in Table B-2. All dose verification results met the protocol criteria of within $100.0 \pm 10.0\%$ of nominal concentration.

C. Homogeneity Determination

The formulations tested in Section III.B for dose verification were tested for homogeneity at the same time. Homogeneity results of the formulations are summarized in Table B-3. All results met the protocol requirements of % RSD $\leq 5.0\%$.

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

D. Stability Determination

Stability of the formulation was determined using 4, 12 and 40 $\mu\text{g}/\text{ml}$ mock formulations prior to the study. The results of the stability study are summarized in Tables B-4 and B-5. The stability results met the protocol criterion of within $100.0 \pm 10.0\%$ of initial concentration. Formulations with concentrations of 4 to 40 $\mu\text{g}/\text{ml}$ were stable for at least 3 days refrigerated (2.5 to 4.0°C) and 1 day at room temperature after refrigeration (20.0 to 23.5°C).

E. Test Article Purity

Chromatographic purity of the test article results are summarized in Table B-6. As shown in Table B-6, the purity value did not change during the study duration, suggesting that the test article is stable for the time period.

IV. CONCLUSIONS

The dose formulations at nominal concentration range of 4.4 to 17.6 $\mu\text{g}/\text{ml}$ was tested for dose concentration and homogeneity during the study period. The results met the protocol criteria of $100.0 \pm 10.0\%$ of nominal concentration and homogeneity of % RSD $\leq 5.0\%$, indicating that the dose formulation had the claimed concentrations and was also homogeneous.

Mock formulations at nominal concentrations of 4 to 40 $\mu\text{g}/\text{ml}$ were tested to determine the formulation stability. The results indicated that formulations at a nominal concentration range of 4 to 40 $\mu\text{g}/\text{ml}$ were stable for at least 3 days refrigerated (2.5 to 4.0°C) and 1 day at room temperature after refrigeration (20.0 to 23.5°C).

Chromatographic purity results supported that the test article was stable during the study period.

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

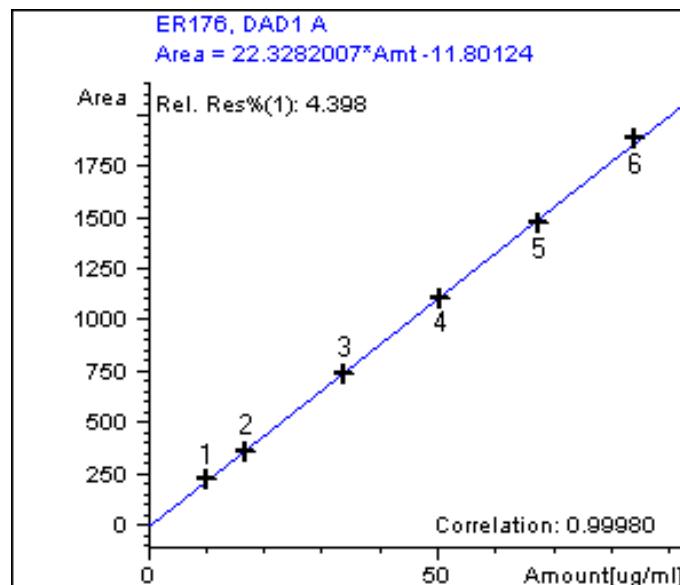


Figure B-1. A representative calibration curve used in the analysis.

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

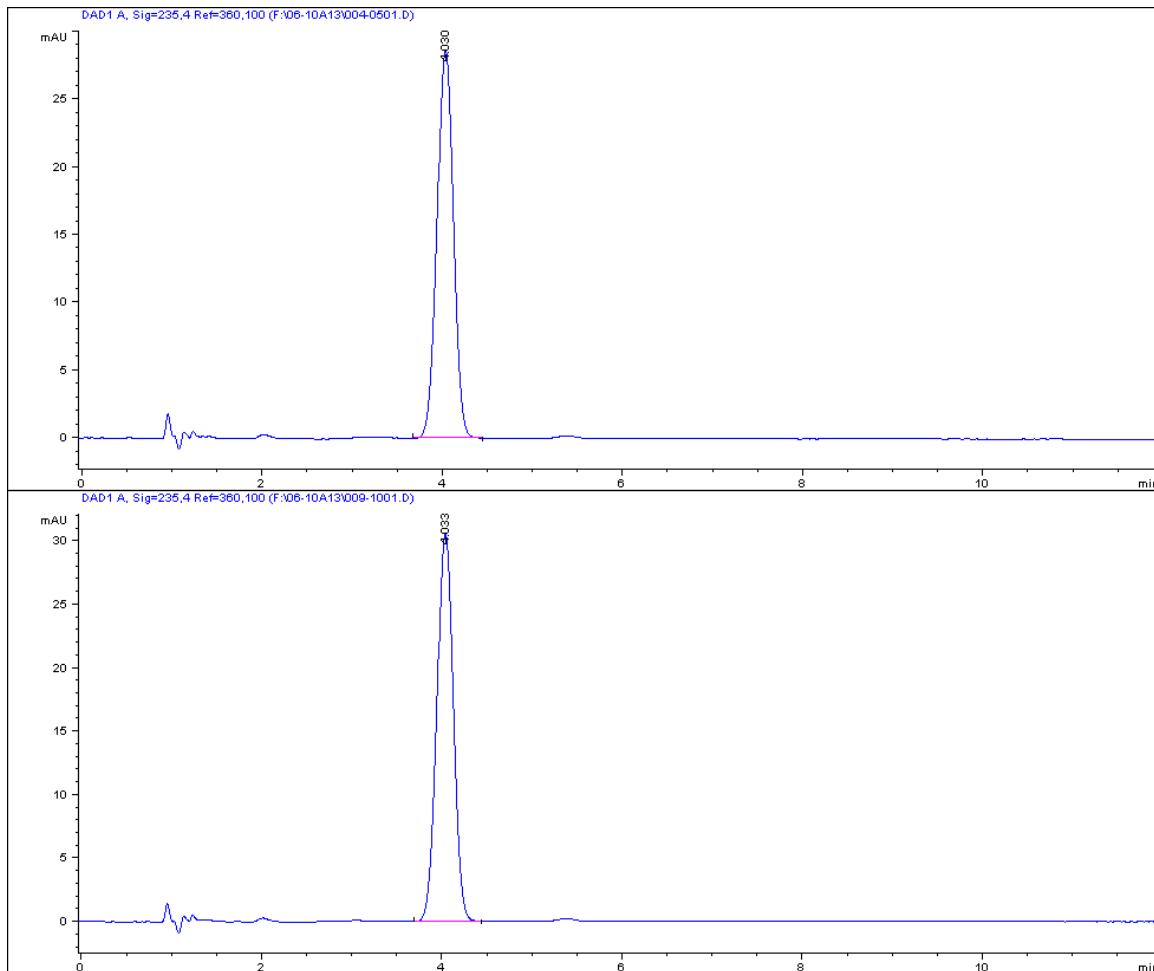


Figure B-2. Representative HPLC chromatograms of test article standard dissolved with the diluent, 10% ethanol/90% saline at 16.822 µg/ml, (top panel) and representative 17.6 µg/ml formulation sample in vehicle (bottom panel). Peaks at ~4.0 min are from the test article, ER176.

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table B-1. System Suitability and Method Performance Results¹

System Suitability (Protocol Criteria)	Experiment	Results	Comments
Repeatability (% RSD ≤ 3.0%)	Stability T = 0 of mock formulation (12 and 40 µg/mL) on 6/3/13	0.2	Pass
	Stability T = 3 day RF + 1 day RT on 6/7/13	0.1	Pass
	Dose verification/homogeneity of dose formulation on 6/10/13	0.1	Pass
	Stability T = 0 of mock formulation (4 µg/mL) on 10/4/13	0.1	Pass
	Stability T = 3 day RF + 1 day RT on 10/8/13	0.2	Pass
	Dose verification/homogeneity of dose formulation on 10/21/13	0.2	Pass
Reproducibility of Std. Throughout the Run (% RSD ≤ 10.0%)	Stability T = 0 of mock formulation (12 and 40 µg/mL) on 6/3/13	3.4	Pass
	Stability T = 3 day RF + 1 day RT on 6/7/13	1.3	Pass
	Dose verification/homogeneity of dose formulation on 6/10/13	1.4	Pass
	Stability T = 0 of mock formulation (4 µg/mL) on 10/4/13	0.5	Pass
	Stability T = 3 day RF + 1 day RT on 10/8/13	0.6	Pass
	Dose verification/homogeneity of dose formulation on 10/21/13	0.4	Pass

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Table B-1. System Suitability and Method Performance Results¹(Continued)

Accuracy Check (Within 100.0 ± 5.0%)	Stability T = 0 of mock formulation (12 and 40 µg/mL) on 6/3/13	100.0	Pass
	Stability T = 3 day RF + 1 day RT on 6/7/13	99.7	Pass
	Dose verification/homogeneity of dose formulation on 6/10/13	99.8	Pass
	Stability T = 0 of mock formulation (4 µg/mL) on 10/4/13	101.8	Pass
	Stability T = 3 day RF + 1 day RT on 10/8/13	100.5	Pass
	Dose verification/homogeneity of dose formulation on 10/21/13	99.1	Pass
Linearity (r ≥ 0.990)	Stability T = 0 of mock formulation (12 and 40 µg/mL) on 6/3/13	0.99981	Pass
	Stability T = 3 day RF + 1 day RT on 6/7/13	0.99982	Pass
	Dose verification/homogeneity of dose formulation on 6/10/13	0.99980	Pass
	Stability T = 0 of mock formulation (4 µg/mL) on 10/4/13	0.99999	Pass
	Stability T = 3 day RF + 1 day RT on 10/8/13	1.00000	Pass
	Dose verification/homogeneity of dose formulation on 10/21/13	0.99999	Pass

¹ Stock Standard solution and calibration standards were used for system suitability and method performance tests. Stock Standard solutions (~80 to 106 µg/ml) were used for accuracy checks. Calibration standards (~2 to 88 µg/ml) were used for other tests. RF: refrigerated; RT: room temperature.

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
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Table B-2. Dose Verification of the Test Article in the Vehicle¹

Dose Level (mg/kg) (Exp Date)	Formulation Concentration (μ g/ml)		Percentage of Nominal (%)	Average Percentage Of Nominal (%)
	Nominal	Actual		
NA (Mock Formulation) (6/3/13)	12	11.8696	98.91	99.0
		11.8987	99.16	
		11.8694	98.91	
	40	40.1384	100.35	100.3
		40.1083	100.27	
		40.0911	100.23	
88.1 (Dose Formulation) (6/10/13)	17.6	17.9295	101.87	101.9
		17.9404	101.93	
		17.9086	101.75	
NA (Mock Formulation) (10/4/13)	4	4.2227	105.57	104.9
		4.1843	104.61	
		4.1818	104.55	
22.0 (Dose Formulation) (10/21/13)	4.4	4.7459	107.86	107.1
		4.7019	106.86	
		4.6872	106.53	
44.1 (Dose Formulation) (10/21/13)	8.8	9.4268	107.12	107.1
		9.4149	106.99	
		18.9408	107.62	
88.1 (Dose Formulation) (10/21/13)	17.6	18.9070	106.43	107.5
		18.9177	107.49	

¹ Results (% nominal) reported are based upon non-rounded numbers. All other values may have been rounded for report entry. This note applies to all the tables in this report.

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Table B-3. Homogeneity of the Test Article in the Vehicle

Exp Date	Formulation Concentration ($\mu\text{g}/\text{ml}$)		Percentage of Nominal (%)	Homogeneity (% RSD)
	Nominal	Actual		
6/3/13 (Mock Formulation)	12 (Top)	11.8696	98.91	0.1
	12 (Middle)	11.8987	99.16	
	12 (Bottom)	11.8694	98.91	
	40 (Top)	40.1384	100.35	0.1
	40 (Middle)	40.1083	100.27	
	40 (Bottom)	40.0911	100.23	
6/10/13 (Dose Formulation)	17.6 (Top)	17.9295	101.87	0.1
	17.6 (Middle)	17.9404	101.93	
	17.6 (Bottom)	17.9086	101.75	
10/4/13 (Mock Formulation)	4 (Top)	4.2227	105.57	0.5
	4 (Middle)	4.1843	104.61	
	4 (Bottom)	4.1818	104.55	
10/21/13 (Dose Formulation)	4.4 (Top)	4.7459	107.86	0.6
	4.4 (Middle)	4.7019	106.86	
	4.4 (Bottom)	4.6872	106.53	
10/21/13 (Dose Formulation)	17.6 (Top)	18.9408	107.62	0.1
	17.6 (Middle)	18.9070	106.43	
	17.6 (Bottom)	18.9177	107.49	

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Table B-4. Stability of the Formulation Based on Nominal Concentration¹

Time Point (Exp Date)	Formulation Concentration (μ g/ml)		Percentage of Nominal (%)	Average Percentage of Nominal (%)
	Nominal	Actual		
T = 0 (6/3/13)	12	11.8696	98.91	99.0
		11.8987	99.16	
		11.8694	98.91	
	40	40.1384	100.35	100.3
		40.1083	100.27	
		40.0911	100.23	
T = 3 d RF + 1 d RT (6/7/13)	12	12.3253	102.71	102.7
		12.3276	102.73	
	40	40.2874	100.72	100.6
		40.1698	100.42	
T = 0 (10/4/13)	4	4.2227	105.57	104.9
		4.1843	104.61	
		4.1818	104.55	
T = 3 d RF + 1 d RT (10/8/13)	4	4.2584	106.46	106.3
		4.2424	106.06	

¹ Results were evaluated against the nominal concentration. The refrigerator temperature (RF) range was from 2.5 to 4.0°C. The room temperature (RT) range was from 20.0 to 23.5°C. RF: refrigerated; RT: room temperature; d: day.

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Table B-5. Stability of the Formulation Based on Initial Concentration¹

Time Point (Exp Date)	Formulation Concentration (μ g/ml)		Percentage of Initial (%)	Average Percentage of Initial (%)
	Nominal (T = 0) / Initial	Actual		
T = 0 (6/3/13)	12	11.8696	N/A	N/A
		11.8987	N/A	
		11.8694	N/A	
	40	40.1384	N/A	N/A
		40.1083	N/A	
		40.0911	N/A	
T = 3 d RF + 1 d RT (6/7/13)	11.879	12.3253	103.75	103.8
		12.3276	103.77	
	40.113	40.2874	100.44	100.3
		40.1698	100.14	
T = 0 (10/4/13)	4	4.2227	N/A	N/A
		4.1843	N/A	
		4.1818	N/A	
T = 3 d RF + 1 d RT (10/8/13)	4.196	4.2584	101.48	101.3
		4.2424	101.10	

¹ Results were evaluated against the initial concentration; therefore, results are not applicable (N/A) for T = 0. See footnotes on Table B-4 for other information.

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
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Table B-6. Purity Evaluation

Experiment Date	Sample Concentration (μg/ml)	Purity (Peak Area %)	Comment
6/3/13	87.592	98.9	No Change
6/10/13	84.108	98.9	
10/21/13	80.760	98.9	

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
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Appendix C

INDIVIDUAL CLINICAL OBSERVATIONS

Individual Clinical Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date														
					1	2	3	4	5	6	7	8	9	1	1	1	1	1	5
1	m	001	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		002	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		003	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		004	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		005	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		006	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Recovery Sacrifice		X
		007	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Recovery Sacrifice		X
		008	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Recovery Sacrifice		X
		009	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Recovery Sacrifice		X
		010	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Recovery Sacrifice		X

General Footnote: . Not Applicable

Severity Codes: X = Present; S = Slight

Group 1 0 ug/kg IV Group 2 88.1 ug/kg IV Group 3 22.0 ug/kg IV
 Group 4 44.1 ug/kg IV Group 5 88.1 ug/kg IV

Individual Clinical Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date														
					1	2	3	4	5	6	7	8	9	1	1	1	1	1	5
2	m	021	No Abnormalities Detected		X	X	X
			Ataxia		S
			Main Sacrifice		.	.	X
		022	No Abnormalities Detected		X	X	X
			Ataxia		S
			Main Sacrifice		.	.	X
		023	No Abnormalities Detected		X	X	X
			Ataxia		S
			Main Sacrifice		.	.	X
		024	No Abnormalities Detected		X	X	X
			Ataxia		S
			Main Sacrifice		.	.	X
		025	No Abnormalities Detected		X	X	X
			Ataxia		S
			Main Sacrifice		.	.	X
		026	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Ataxia		S
			Recovery Sacrifice		X	.
		027	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Ataxia		S
			Recovery Sacrifice		X	.
		028	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Ataxia		S
			Recovery Sacrifice		X	.
		029	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Ataxia		S
			Recovery Sacrifice		X	.
		030	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Ataxia		S
			Recovery Sacrifice		X	.

General Footnote: . Not Applicable

Severity Codes: X = Present; S = Slight

Group 1 0 ug/kg IV Group 2 88.1 ug/kg IV Group 3 22.0 ug/kg IV
 Group 4 44.1 ug/kg IV Group 5 88.1 ug/kg IV

Individual Clinical Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date													
					1	2	3	4	5	6	7	8	9	1	1	1	1	
3	m	041	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		042	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		043	No Abnormalities Detected		X	X	X
			Fecal Stain		S
			Soft Stool		S
			Main Sacrifice		.	.	X
		044	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		045	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		046	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		047	No Abnormalities Detected		X	X	X
			Soft Stool		S
			Main Sacrifice		.	.	X
		048	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		049	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		050	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X

General Footnote: . Not Applicable

Severity Codes: X = Present; S = Slight

Group 1 0 ug/kg IV Group 2 88.1 ug/kg IV Group 3 22.0 ug/kg IV
 Group 4 44.1 ug/kg IV Group 5 88.1 ug/kg IV

Individual Clinical Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date												
					1	2	3	4	5	6	7	8	9	1	1	1	1
4	m	061	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		062	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		063	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		064	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		065	No Abnormalities Detected		X	X	X
			Ataxia		S
			Main Sacrifice		.	.	X
		066	No Abnormalities Detected		X	X	X
			Hyperthermia		S
			Main Sacrifice		.	.	X
		067	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		068	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		069	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		070	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X

General Footnote: . Not Applicable

Severity Codes: X = Present; S = Slight

Group 1 0 ug/kg IV Group 2 88.1 ug/kg IV Group 3 22.0 ug/kg IV
 Group 4 44.1 ug/kg IV Group 5 88.1 ug/kg IV

Individual Clinical Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date												
					1	2	3	4	5	6	7	8	9	1	1	1	1
5	m	081	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		082	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		083	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		084	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		085	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		086	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		087	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		088	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		089	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		090	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X

General Footnote: . Not Applicable

Severity Codes: X = Present; S = Slight

Group 1 0 ug/kg IV Group 2 88.1 ug/kg IV Group 3 22.0 ug/kg IV
 Group 4 44.1 ug/kg IV Group 5 88.1 ug/kg IV

Individual Clinical Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date													
					1	2	3	4	5	6	7	8	9	1	1	1	1	1
1	f	011	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		012	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		013	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		014	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		015	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		016	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Recovery Sacrifice		X
		017	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Recovery Sacrifice		X
		018	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Recovery Sacrifice		X
		019	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Recovery Sacrifice		X
		020	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Recovery Sacrifice		X

General Footnote: . Not Applicable

Severity Codes: X = Present; S = Slight

Group 1 0 ug/kg IV Group 2 88.1 ug/kg IV Group 3 22.0 ug/kg IV
 Group 4 44.1 ug/kg IV Group 5 88.1 ug/kg IV

Individual Clinical Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date														
					1	2	3	4	5	6	7	8	9	1	1	1	1	1	5
2	f	031	No Abnormalities Detected		X	X	X
			Ataxia		S
			Main Sacrifice		.	.	X
		032	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		033	No Abnormalities Detected		X	X	X
			Ataxia		S
			Main Sacrifice		.	.	X
		034	No Abnormalities Detected		X	X	X
			Ataxia		S
			Main Sacrifice		.	.	X
		035	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		036	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Hyperactivity		S
			Recovery Sacrifice		X
		037	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Ataxia		S
			Recovery Sacrifice		X
		038	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Ataxia		S
			Recovery Sacrifice		X
		039	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Ataxia		S
			Recovery Sacrifice		X
		040	No Abnormalities Detected		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Recovery Sacrifice		X

General Footnote: . Not Applicable

Severity Codes: X = Present; S = Slight

Group 1 0 ug/kg IV Group 2 88.1 ug/kg IV Group 3 22.0 ug/kg IV
 Group 4 44.1 ug/kg IV Group 5 88.1 ug/kg IV

Individual Clinical Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date												
					1	2	3	4	5	6	7	8	9	1	1	1	1
3	f	051	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		052	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		053	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		054	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		055	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		057	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		058	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		059	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		060	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		056	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X

General Footnote: . Not Applicable

Severity Codes: X = Present; S = Slight

Group 1 0 ug/kg IV Group 2 88.1 ug/kg IV Group 3 22.0 ug/kg IV
 Group 4 44.1 ug/kg IV Group 5 88.1 ug/kg IV

Individual Clinical Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

			Day numbers relative to Start Date															
Group	Sex	Animal	Clinical Sign	Site	1	2	3	4	5	6	7	8	9	1	1	1	1	1
4	f	071	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		072	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		073	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		074	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		075	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		076	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		077	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		078	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		079	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		080	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X

General Footnote: . Not Applicable

Severity Codes: X = Present; S = Slight

Group 1 0 ug/kg IV Group 2 88.1 ug/kg IV Group 3 22.0 ug/kg IV
 Group 4 44.1 ug/kg IV Group 5 88.1 ug/kg IV

Individual Clinical Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Group	Sex	Animal	Clinical Sign	Site	Day numbers relative to Start Date												
					1	2	3	4	5	6	7	8	9	1	1	1	1
5	f	091	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		092	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		093	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		094	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		095	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		096	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		097	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		098	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		099	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X
		100	No Abnormalities Detected		X	X	X
			Main Sacrifice		.	.	X

General Footnote: . Not Applicable

Severity Codes: X = Present; S = Slight

Group 1 0 ug/kg IV Group 2 88.1 ug/kg IV Group 3 22.0 ug/kg IV
 Group 4 44.1 ug/kg IV Group 5 88.1 ug/kg IV

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
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Appendix D
INDIVIDUAL BODY WEIGHTS

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Appendix D-1
INDIVIDUAL BODY WEIGHTS

Individual Body Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Body Weight (g)

Group 1 0 ug/kg IV	Day(s) Relative to Start Date		
	1	3	15
001	290	304	-
002	275	289	-
003	276	288	-
004	261	274	-
005	272	285	-
006	279	285	358
007	283	289	373
008	274	272	319
009	284	292	373
010	266	267	315
Mean	276.0	284.5	347.6
SD	8.6	10.9	28.6
N	10	10	5

General Footnote: [- Not Applicable]

Individual Body Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Body Weight (g)

Group 2 88.1 ug/kg IV	Day(s) Relative to Start Date		
	1	3	15
021	288	301	-
022	271	281	-
023	272	290	-
024	290	305	-
025	276	295	-
026	280	282	351
027	278	282	334
028	284	294	365
029	273	284	364
030	283	291	383
Mean	279.5	290.5	359.4
SD	6.7	8.4	18.2
N	10	10	5

General Footnote: [- Not Applicable]

Individual Body Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Body Weight (g)

Group 3 22.0 ug/kg IV	Day(s) Relative to Start Date		
	1	3	15
041	252	268	-
042	264	277	-
043	251	238	-
044	244	259	-
045	251	265	-
046	254	271	-
047	238	254	-
048	255	267	-
049	249	267	-
050	245	257	-
Mean	250.3	262.3	-
SD	7.1	10.9	-
N	10	10	-

General Footnote: [- Not Applicable]

Individual Body Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Body Weight (g)

Group 4 44.1 ug/kg IV	Day(s) Relative to Start Date		
	1	3	15
061	249	264	-
062	249	269	-
063	245	262	-
064	251	266	-
065	246	265	-
066	246	260	-
067	243	254	-
068	262	275	-
069	254	271	-
070	254	275	-
Mean	249.9	266.1	-
SD	5.6	6.6	-
N	10	10	-

General Footnote: [- Not Applicable]

Individual Body Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Body Weight (g)

Group 5 88.1 ug/kg IV	Day(s) Relative to Start Date		
	1	3	15
081	256	276	-
082	247	263	-
083	248	261	-
084	241	276	-
085	256	256	-
086	250	261	-
087	248	263	-
088	245	264	-
089	252	269	-
090	262	277	-
Mean	250.5	266.6	-
SD	6.2	7.4	-
N	10	10	-

General Footnote: [- Not Applicable]

Individual Body Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Body Weight (g)

Group 1 0 ug/kg IV	Day(s) Relative to Start Date		
	1	3	15
011	186	193	-
012	188	190	-
013	190	192	-
014	186	193	-
015	182	190	-
016	177	179	205
017	189	190	233
018	192	194	225
019	196	200	252
020	185	188	228
Mean	187.1	190.9	228.6
SD	5.3	5.3	16.9
N	10	10	5

General Footnote: [- Not Applicable]

Individual Body Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Body Weight (g)

Group 2 88.1 ug/kg IV	Day(s) Relative to Start Date		
	1	3	15
031	168	181	-
032	176	187	-
033	189	201	-
034	189	193	-
035	178	175	-
036	185	186	228
037	182	181	221
038	188	186	225
039	179	190	232
040	185	193	218
Mean	181.9	187.3	224.8
SD	6.7	7.4	5.5
N	10	10	5

General Footnote: [- Not Applicable]

Individual Body Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Body Weight (g)

Group 3 22.0 ug/kg IV	Day(s) Relative to Start Date		
	1	3	15
051	169	183	-
052	160	166	-
053	180	180	-
054	171	182	-
055	186	183	-
057	178	182	-
058	166	170	-
059	171	177	-
060	186	191	-
056	164	172	-
Mean	173.1	178.6	-
SD	9.0	7.4	-
N	10	10	-

General Footnote: [- Not Applicable]

Individual Body Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Body Weight (g)

Group 4 44.1 ug/kg IV	Day(s) Relative to Start Date		
	1	3	15
071	172	174	-
072	173	185	-
073	177	181	-
074	169	174	-
075	179	175	-
076	169	168	-
077	188	199	-
078	186	181	-
079	162	175	-
080	172	184	-
Mean	174.7	179.6	-
SD	8.0	8.6	-
N	10	10	-

General Footnote: [- Not Applicable]

Individual Body Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Body Weight (g)

Group 5 88.1 ug/kg IV	Day(s) Relative to Start Date		
	1	3	15
091	166	167	-
092	163	171	-
093	185	193	-
094	171	175	-
095	174	177	-
096	174	185	-
097	166	183	-
098	188	193	-
099	173	176	-
100	178	188	-
Mean	173.8	180.8	-
SD	8.1	9.0	-
N	10	10	-

General Footnote: [- Not Applicable]

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Appendix D-2

INDIVIDUAL BODY WEIGHT CHANGES

Individual Body Weight Changes

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Absolute Weight Gain (g)

Group 1 0 ug/kg IV	Day(s) Relative to Start Date	
	1 → 3	3 → 15
001	14	-
002	14	-
003	12	-
004	13	-
005	13	-
006	6	73
007	6	84
008	-2	47
009	8	81
010	1	48

General Footnote: [- Not Applicable]

Individual Body Weight Changes

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Absolute Weight Gain (g)

Group 2 88.1 ug/kg IV	Day(s) Relative to Start Date	
	1 → 3	3 → 15
021	13	-
022	10	-
023	18	-
024	15	-
025	19	-
026	2	69
027	4	52
028	10	71
029	11	80
030	8	92

General Footnote: [- Not Applicable]

Individual Body Weight Changes

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Absolute Weight Gain (g)

Group 3 22.0 ug/kg IV	Day(s) Relative to Start Date	
	1 → 3	3 → 15
041	16	-
042	13	-
043	-13	-
044	15	-
045	14	-
046	17	-
047	16	-
048	12	-
049	18	-
050	12	-

General Footnote: [- Not Applicable]

Individual Body Weight Changes

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Absolute Weight Gain (g)

Group 4 44.1 ug/kg IV	Day(s) Relative to Start Date	
	1 → 3	3 → 15
061	15	-
062	20	-
063	17	-
064	15	-
065	19	-
066	14	-
067	11	-
068	13	-
069	17	-
070	21	-

General Footnote: [- Not Applicable]

Individual Body Weight Changes

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Absolute Weight Gain (g)

Group 5 88.1 ug/kg IV	Day(s) Relative to Start Date	
	1 → 3	3 → 15
081	20	-
082	16	-
083	13	-
084	35	-
085	0	-
086	11	-
087	15	-
088	19	-
089	17	-
090	15	-

General Footnote: [- Not Applicable]

Individual Body Weight Changes

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Absolute Weight Gain (g)

Group 1 0 ug/kg IV	Day(s) Relative to Start Date	
	1 → 3	3 → 15
011	7	-
012	2	-
013	2	-
014	7	-
015	8	-
016	2	26
017	1	43
018	2	31
019	4	52
020	3	40

General Footnote: [- Not Applicable]

Individual Body Weight Changes

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Absolute Weight Gain (g)

Group 2 88.1 ug/kg IV	Day(s) Relative to Start Date	
	1 → 3	3 → 15
031	13	-
032	11	-
033	12	-
034	4	-
035	-3	-
036	1	42
037	-1	40
038	-2	39
039	11	42
040	8	25

General Footnote: [- Not Applicable]

Individual Body Weight Changes

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Absolute Weight Gain (g)

Group 3 22.0 ug/kg IV	Day(s) Relative to Start Date	
	1 → 3	3 → 15
051	14	-
052	6	-
053	0	-
054	11	-
055	-3	-
057	4	-
058	4	-
059	6	-
060	5	-
056	8	-

General Footnote: [- Not Applicable]

Individual Body Weight Changes

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Absolute Weight Gain (g)

Group 4 44.1 ug/kg IV	Day(s) Relative to Start Date	
	1 → 3	3 → 15
071	2	-
072	12	-
073	4	-
074	5	-
075	-4	-
076	-1	-
077	11	-
078	-5	-
079	13	-
080	12	-

General Footnote: [- Not Applicable]

Individual Body Weight Changes

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Absolute Weight Gain (g)

Group 5 88.1 ug/kg IV	Day(s) Relative to Start Date	
	1 → 3	3 → 15
091	1	-
092	8	-
093	8	-
094	4	-
095	3	-
096	11	-
097	17	-
098	5	-
099	3	-
100	10	-

General Footnote: [- Not Applicable]

Individual Body Weight Changes

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Key Page

General Footnotes

- Not Applicable

Measurement Descriptions

<u>Headings Used</u>	<u>Description</u>
Absolute Weight Gain (g)	Absolute Weight Gain (g)

Group Information

<u>Short Name</u>	<u>Long Name</u>	<u>Report Headings 1-4</u>		
1	Vehicle	Group 1	0	ug/kg IV
2	ER176	Group 2	88.1	ug/kg IV
3	ER176 (25x)	Group 3	22.0	ug/kg IV
4	ER176 (50x)	Group 4	44.1	ug/kg IV
5	ER176 (100x)	Group 5	88.1	ug/kg IV

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Appendix E

INDIVIDUAL FOOD CONSUMPTION

Individual Food Consumption

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Total Food Consumption (g)

Group 1 0 ug/kg IV	Day(s) Relative to Start Date		
	1 → 2	6 → 7	8 → 9
001	22.7	-	-
002	22.7	-	-
003	22.7	-	-
004	21.5	-	-
005	21.5	-	-
006	24.7	22.7	22.3
007	24.7	22.7	22.3
008	24.7	22.7	22.3
009	24.0	23.5	23.5
010	24.0	23.5	23.5
Mean	23.30	23.00	22.80
SD	1.26	0.46	0.64
N	10	5	5

General Footnote: [- Not Applicable]

Individual Food Consumption

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Total Food Consumption (g)

Group 2 88.1 ug/kg IV	Day(s) Relative to Start Date		
	1 → 2	6 → 7	8 → 9
021	26.7	-	-
022	26.7	-	-
023	26.7	-	-
024	25.5	-	-
025	25.5	-	-
026	24.7	23.0	21.3
027	24.7	23.0	21.3
028	24.7	23.0	21.3
029	24.0	24.5	23.0
030	24.0	24.5	23.0
Mean	25.30	23.60	22.00
SD	1.07	0.82	0.91
N	10	5	5

General Footnote: [- Not Applicable]

Individual Food Consumption

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Total Food Consumption (g)

Group 1 0 ug/kg IV	Day(s) Relative to Start Date		
	1 → 2	6 → 7	8 → 9
011	12.0	-	-
012	12.0	-	-
013	12.0	-	-
014	14.5	-	-
015	14.5	-	-
016	15.7	14.7	17.7
017	15.7	14.7	17.7
018	15.7	14.7	17.7
019	15.5	15.0	18.5
020	15.5	15.0	18.5
Mean	14.30	14.80	18.00
SD	1.65	0.18	0.46
N	10	5	5

General Footnote: [- Not Applicable]

Individual Food Consumption

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Total Food Consumption (g)

Group 2 88.1 ug/kg IV	Day(s) Relative to Start Date		
	1 → 2	6 → 7	8 → 9
031	12.3	-	-
032	12.3	-	-
033	12.3	-	-
034	15.0	-	-
035	15.0	-	-
036	15.0	15.7	17.3
037	15.0	15.7	17.3
038	15.0	15.7	17.3
039	16.5	23.0	19.5
040	16.5	23.0	19.5
Mean	14.50	18.60	18.20
SD	1.61	4.02	1.19
N	10	5	5

General Footnote: [- Not Applicable]

Individual Food Consumption

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Key Page

General Footnotes

- Not Applicable

Measurement Descriptions

<u>Headings Used</u>	<u>Description</u>
Total Food Consumption	Total Food Consumption

Measurement/Statistics

<u>Measurement</u>	<u>Descriptive</u>
Total Food Consumption	Mean
	Standard Deviation
	Count (N)

Group Information

<u>Short Name</u>	<u>Long Name</u>	<u>Report Headings 1-4</u>		
1	Vehicle	Group 1	0	ug/kg IV
2	ER176	Group 2	88.1	ug/kg IV

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Appendix F

INDIVIDUAL CLINICAL PATHOLOGY

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

INDIVIDUAL CLINICAL HEMATOLOGY DATA

SRI Study No. M038-13

INSTRUMENT USED		ADVIA 120										INTERVAL		Day 3						SEX		Male					
ANALYSIS PERFORMED BY		RH										REVIEWED BY		NC						SPECIES		Rat (SD)					
Group	Animal ID	WBC (X10 ³ /uL)	RBC (X10 ⁶ /uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCC (g/dL)	CHC (g/dL)	RDW (%)	PLC (X10 ³ /uL)	MPV (fL)	NEUT (%)	LYMPH (%)	MONO (%)	EOS (%)	BASO (%)	BAND (%)	ANS (X10 ³ /uL)	ALY (X10 ³ /uL)	AMO (X10 ³ /uL)	AEO (X10 ³ /uL)	ABA (X10 ³ /uL)	ANB (X10 ³ /uL)	RET (%)	REA (X10 ⁹ /L)	Comment Codes
Group 1 Vehicle 0 ug/kg IV	001	7.88	6.32	12.9	40.9	64.7	20.5	31.6	na	12.8	840	6.4	15.9	78.0	5.0	0.8	0.4	na	1.25	6.15	0.39	0.06	0.03	na	5.98	377.8	na
	002	12.10	6.05	12.3	38.6	63.9	20.4	31.9	na	12.7	919	7.6	15.0	70.0	14.0	0.0	0.0	0.0	1.82	8.47	1.69	0.00	0.00	0.00	6.42	388.2	na
	003	12.76	6.86	14.0	43.8	63.9	20.4	32.0	na	12.5	908	7.3	14.0	83.0	2.0	0.6	0.5	na	1.78	10.60	0.25	0.07	0.06	na	5.22	368.5	na
	004	10.44	6.56	13.2	41.9	63.9	20.1	31.5	na	12.1	845	7.3	9.4	86.4	3.3	0.6	0.4	na	0.98	9.01	0.34	0.06	0.04	na	5.28	346.5	na
	005	9.93	7.11	14.8	46.7	65.6	20.8	31.7	na	12.4	837	7.1	13.6	79.7	5.5	1.0	0.3	na	1.35	7.91	0.54	0.10	0.03	na	4.87	346.6	na
Group 2 ER176 88.1 ug/kg IV	021	11.49	6.55	12.9	41.2	63.0	19.7	31.3	na	12.6	1247	6.7	18.2	76.7	3.9	0.8	0.5	na	2.09	8.81	0.45	0.09	0.05	na	6.03	394.7	na
	022	12.88	6.79	14.2	44.8	65.9	20.8	31.6	na	12.0	607	7.8	11.3	85.2	2.5	0.6	0.3	na	1.46	10.96	0.33	0.08	0.04	na	5.25	356.6	na
	023	13.48	6.51	14.1	44.3	68.1	21.6	31.8	na	13.0	1056	7.4	17.6	74.2	6.8	1.0	0.4	na	2.37	10.00	0.91	0.14	0.05	na	8.74	569.1	na
	024	10.69	6.95	14.5	45.7	65.8	20.9	31.7	na	13.2	908	7.2	14.7	80.1	4.0	0.7	0.5	na	1.57	8.56	0.43	0.07	0.05	na	5.99	416.9	na
	025	13.08	6.65	13.5	43.1	64.8	20.3	31.4	na	13.2	831	7.2	20.1	76.0	3.1	0.4	0.4	na	2.63	9.94	0.41	0.05	0.05	na	5.99	398.9	na

Comment Codes: 10 = Normal Morphology; 1 = Platelet Clumps Seen, 2 = Malarial Parasites Seen, 3 = Platelet Decrease, 4 = Platelet Increase, 90 = Abnormal

2X = Anisocytosis, 3X = Poikilocytosis, 4X = Hypochromia, 5X = Polychromasia/Hyperchromia, 6X = Microcytosis, 7X = Macrocytosis, (X = Degree 1, 2, 3, or 4; Degree Codes 1 = 1+, 2 = 2+, 3 = 3+, 4 = 4+).

91 = Few target cells

na = Not Applicable

Result obtained by repeat analysis:

CBC/DIFF: #003

Via Manual (Manual differential performed by DV)

Manual differential: #002. Absolute differential results for these samples were calculated using computer formula and then verified manually.

Atypical lymphocytes seen via manual differential: #002 (1.0%).

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

INDIVIDUAL CLINICAL HEMATOLOGY DATA

SRI Study No. M038-13

INSTRUMENT USED		ADVIA 120										INTERVAL		Day 15					SEX		Male						
ANALYSIS PERFORMED BY		LD										REVIEWED BY		NC					SPECIES		Rat (SD)						
Group	Animal ID	WBC (X10 ³ /uL)	RBC (X10 ⁶ /uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCC (g/dL)	CHC (g/dL)	RDW (%)	PLC (X10 ³ /uL)	MPV (fL)	NEUT (%)	LYMPH (%)	MONO (%)	EOS (%)	BAZO (%)	BAND (%)	ANS (X10 ³ /uL)	ALY (X10 ³ /uL)	AMO (X10 ³ /uL)	AEO (X10 ³ /uL)	ABA (X10 ³ /uL)	ANB (X10 ³ /uL)	RET (%)	REA (X10 ³ /L)	Comment Codes
Group 1 Vehicle 0 ug/kg IV	006	10.49	7.47	15.0	46.0	61.6	20.1	32.7	na	11.8	876	6.7	11.0	84.5	3.7	0.5	0.3	na	1.16	8.86	0.39	0.05	0.03	na	2.84	212.4	na
	007	12.23	8.49	16.1	50.3	59.2	18.9	31.9	na	11.8	809	6.9	10.9	85.6	2.4	0.5	0.6	na	1.34	10.46	0.30	0.06	0.07	na	2.96	251.6	na
	008	7.58	7.85	15.4	47.0	59.8	19.6	32.8	na	11.3	967	6.5	12.7	84.7	1.8	0.6	0.2	na	0.96	6.42	0.14	0.04	0.02	na	2.41	189.6	na
	009	12.69	7.39	14.5	44.2	59.9	19.6	32.8	na	11.2	831	6.2	8.9	88.9	1.2	0.4	0.5	na	1.13	11.28	0.15	0.06	0.07	na	2.93	216.4	na
	010	9.68	7.94	15.3	46.7	58.9	19.2	32.7	na	11.0	748	7.2	12.3	81.7	4.8	0.8	0.4	na	1.19	7.91	0.46	0.07	0.04	na	2.16	171.1	na
Group 2 ER176 88.1 ug/kg IV	026	11.77	7.40	15.0	46.1	62.3	20.3	32.6	na	11.2	817	6.8	10.1	87.0	1.6	0.7	0.6	na	1.18	10.24	0.18	0.08	0.07	na	2.58	190.6	na
	027	13.21	7.76	14.7	43.6	56.3	18.9	33.6	na	11.3	745	7.4	8.9	88.6	1.4	0.6	0.6	na	1.17	11.70	0.18	0.07	0.08	na	1.95	151.1	na
	028	11.42	7.73	15.8	48.7	63.0	20.5	32.5	na	11.3	967	6.5	5.5	92.1	1.1	0.7	0.5	na	0.63	10.52	0.12	0.08	0.05	na	2.19	169.7	na
	029	9.63	6.86	14.1	44.0	64.2	20.5	32.0	na	11.9	808	7.7	13.0	83.4	2.4	0.8	0.4	na	1.25	8.04	0.23	0.08	0.03	na	3.19	218.7	na
	030	7.84	7.78	15.4	47.3	60.8	19.8	32.5	na	11.9	862	7.1	16.4	79.9	2.2	1.0	0.4	na	1.29	6.26	0.17	0.08	0.03	na	3.93	305.6	na

Comment Codes: 10 = Normal Morphology, 1 = Platelet Clumps Seen, 2 = Malarial Parasites Seen, 3 = Platelet Decrease, 4 = Platelet Increase, 90 = Abnormal

2X = Anisocytosis, 3X = Poikilocytosis, 4X = Hypochromia, 5X = Polychromasia/Hyperchromia, 6X = Microcytosis, 7X = Macrocytosis, (X = Degree 1, 2, 3, or 4; Degree Codes 1 = 1+, 2 = 2+, 3 = 3+, 4 = 4+).

91 = Few target cells

na = Not Applicable

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

INDIVIDUAL CLINICAL HEMATOLOGY DATA

SRI Study No. M038-13

INSTRUMENT USED		ADVIA 120										INTERVAL		Day 3						SEX		Female					
ANALYSIS PERFORMED BY		RH										REVIEWED BY		NC						SPECIES		Rat (SD)					
Group	Animal ID	WBC (X10 ³ /uL)	RBC (X10 ⁶ /uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCC (g/dL)	CHC (g/dL)	RDW (%)	PLC (X10 ³ /uL)	MPV (fL)	NEUT (%)	LYMPH (%)	MONO (%)	EOS (%)	BASO (%)	BAND (%)	ANS (X10 ³ /uL)	ALY (X10 ³ /uL)	AMO (X10 ³ /uL)	AEO (X10 ³ /uL)	ABA (X10 ³ /uL)	ANB (X10 ³ /uL)	RET (%)	REI (X10 ⁹ /L)	Comment Codes
Group 1 Vehicle 0 ug/kg IV	011	11.40	6.65	13.6	42.4	63.8	20.5	32.1	na	11.4	808	7.6	5.1	92.2	1.8	0.5	0.3	na	0.58	10.51	0.21	0.06	0.04	na	3.84	255.5	na
	012	10.64	6.87	13.7	43.3	63.0	20.0	31.7	na	11.4	1125	7.1	9.2	88.1	2.0	0.4	0.3	na	0.98	9.36	0.21	0.05	0.03	na	5.58	388.1	na
	013	8.06	6.65	12.9	39.9	60.0	19.4	32.3	na	11.9	727	6.8	7.0	89.0	4.0	0.0	0.0	0.0	0.56	7.17	0.32	0.00	0.00	0.00	3.70	245.8	na
	014	13.22	7.03	13.9	43.4	61.8	19.8	32.1	na	12.0	1173	6.2	9.4	87.0	2.6	0.5	0.4	na	1.25	11.51	0.34	0.06	0.06	na	3.20	224.8	na
	015	9.00	6.85	13.3	42.3	61.7	19.5	31.6	na	11.8	914	7.1	6.2	91.3	1.7	0.4	0.4	na	0.56	8.21	0.15	0.04	0.04	na	4.02	275.2	na
Group 2 ER176 88.1 ug/kg IV	031	9.80	6.77	13.6	41.2	60.8	20.1	33.0	na	10.9	806	7.2	7.2	88.8	2.7	0.8	0.4	na	0.70	8.71	0.26	0.08	0.04	na	2.68	181.5	na
	032	8.36	7.18	14.5	45.1	62.9	20.2	32.2	na	11.0	1014	7.4	11.3	84.0	3.4	1.0	0.3	na	0.95	7.02	0.29	0.08	0.03	na	3.31	237.3	na
	033	10.44	7.17	14.7	44.4	62.0	20.5	33.1	na	12.1	372	7.7	8.2	85.8	5.4	0.4	0.4	na	0.85	8.95	0.56	0.04	0.04	na	3.25	232.6	na
	034	8.88	6.55	14.1	43.9	67.1	21.6	32.2	na	11.3	852	7.3	8.6	83.2	7.5	0.6	0.3	na	0.76	7.38	0.66	0.05	0.03	na	4.41	288.7	na
	035	6.45	6.60	13.3	40.1	60.8	20.1	33.1	na	12.0	1379	7.4	9.1	88.2	1.8	0.5	0.3	na	0.59	5.69	0.12	0.03	0.02	na	4.46	294.1	na

Comment Codes: 10 = Normal Morphology; 1 = Platelet Clumps Seen, 2 = Malarial Parasites Seen, 3 = Platelet Decrease, 4 = Platelet Increase, 90 = Abnormal

2X = Anisocytosis, 3X = Poikilocytosis, 4X = Hypochromia, 5X = Polychromasia/Hyperchromia, 6X = Microcytosis, 7X = Macrocytosis, (X = Degree 1, 2, 3, or 4; Degree Codes 1 = 1+, 2 = 2+, 3 = 3+, 4 = 4+).

91 = Few target cells

na = Not Applicable

Result obtained by repeat analysis:

Via Manual (Manual differential performed by DV)

CBC/DIFF: #012

Manual differential: #013. Absolute differential results for these samples were calculated using computer formula and then verified manually.

Confirmed by repeat analysis:

CBC: #013

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

INDIVIDUAL CLINICAL HEMATOLOGY DATA

SRI Study No. M038-13

INSTRUMENT USED		ADVIA 120										INTERVAL		Day 15					SEX		Female						
ANALYSIS PERFORMED BY		LD										REVIEWED BY		NC					SPECIES		Rat (SD)						
Group	Animal ID	WBC (X10 ³ /uL)	RBC (X10 ⁶ /uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCC (g/dL)	CHC (g/dL)	RDW (%)	PLC (X10 ³ /uL)	MPV (fL)	NEUT (%)	LYMPH (%)	MONO (%)	EOS (%)	BAZO (%)	BAND (%)	ANS (X10 ³ /uL)	ALY (X10 ³ /uL)	AMO (X10 ³ /uL)	AEO (X10 ³ /uL)	ABA (X10 ³ /uL)	ANB (X10 ³ /uL)	RET (%)	REA (X10 ³ /L)	Comment Codes
Group 1 Vehicle 0 ug/kg IV	016	8.00	7.08	13.2	40.4	57.1	18.6	32.6	na	11.1	746	7.3	6.9	89.5	2.5	0.6	0.5	na	0.55	7.16	0.20	0.05	0.04	na	2.30	163.0	na
	017	7.84	7.45	13.7	42.4	56.9	18.4	32.3	na	11.4	984	6.3	8.2	88.6	2.2	0.5	0.4	na	0.65	6.96	0.17	0.04	0.03	na	2.75	205.2	na
	018	10.61	7.22	14.3	42.6	59.0	19.8	33.5	na	10.5	901	6.6	8.6	88.6	1.9	0.5	0.3	na	0.91	9.40	0.21	0.05	0.03	na	1.71	123.1	na
	019	12.08	6.67	13.2	39.0	58.5	19.8	33.8	na	11.2	625	7.6	8.5	88.9	1.7	0.6	0.3	na	1.03	10.74	0.21	0.07	0.04	na	3.06	188.0	na
	020	11.58	7.99	15.3	45.0	56.3	19.1	34.0	na	11.3	773	7.7	11.6	84.2	3.0	0.7	0.5	na	1.34	9.76	0.34	0.08	0.06	na	2.50	199.8	na
Group 2 ER176 88.1 ug/kg IV	036	7.53	7.09	14.0	41.4	58.4	19.7	33.7	na	10.6	716	7.7	13.6	83.1	1.9	1.1	0.4	na	1.02	6.25	0.14	0.08	0.03	na	2.72	192.9	na
	037	11.00	7.39	13.8	41.6	56.3	18.7	33.1	na	11.1	377	8.1	8.0	88.8	2.1	0.7	0.4	na	0.88	9.78	0.23	0.07	0.04	na	1.95	144.4	na
	038	10.31	7.18	14.7	44.3	61.7	20.5	33.3	na	11.2	920	7.4	10.8	84.6	3.5	0.7	0.4	na	1.11	8.72	0.36	0.07	0.05	na	3.85	276.2	na
	039	12.24	7.13	14.2	43.0	60.2	19.9	33.1	na	10.6	834	7.5	14.5	83.0	1.3	0.7	0.5	na	1.77	10.16	0.16	0.08	0.06	na	2.41	172.3	na
	040	10.95	7.77	15.1	44.7	57.6	19.5	33.8	na	10.7	807	6.8	6.1	91.5	1.3	0.7	0.4	na	0.67	10.02	0.14	0.08	0.04	na	1.56	120.9	na

Comment Codes: 10 = Normal Morphology, 1 = Platelet Clumps Seen, 2 = Malarial Parasites Seen, 3 = Platelet Decrease, 4 = Platelet Increase, 90 = Abnormal

2X = Anisocytosis, 3X = Poikilocytosis, 4X = Hypochromia, 5X = Polychromasia/Hyperchromia, 6X = Microcytosis, 7X = Macrocytosis, (X = Degree 1, 2, 3, or 4; Degree Codes 1 = 1+, 2 = 2+, 3 = 3+, 4 = 4+).

91 = Few target cells

na = Not Applicable

Result obtained by repeat analysis:

CBC/DIFF: #019

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

INDIVIDUAL CLINICAL CHEMISTRY DATA

SRI Study No. M038-13

INSTRUMENT USED			Cobas c-501		INTERVAL			Day 3		SEX			Male							
ANALYSIS PERFORMED BY			DV		REVIEWED BY			NC		SPECIES			Rat (SD)							
Group	Animal ID	BUN (mg/dL)	CRE (mg/dL)	GLU (mg/dL)	AST (U/L)	ALT (U/L)	ALP (U/L)	TBI (mg/dL)	SOD (mEq/L)	POT (mEq/L)	CHL (mEq/L)	CAL (mg/dL)	PHO (mg/dL)	TPR (g/dL)	ALB (g/dL)	GLO (g/dL)	AGR	CHO (mg/dL)	TRI (mg/dL)	
Group 1 Vehicle 0 ug/kg IV	001	14	0.20	137	68	44	317	<0.10	142	5.5	98	11.8	11.0	6.1	4.0	2.1	2	109	315	
	002	14	0.22	143	80	53	334	<0.10	142	5.3	98	12.5	10.6	6.0	4.1	1.9	2	72	128	
	003	12	0.19	109	81	49	372	<0.10	143	6.7	98	11.8	11.8	6.4	4.4	2.0	2	82	128	
	004	14	0.20	141	94	45	291	<0.10	144	5.5	100	11.9	10.4	5.9	3.9	2.0	2	79	168	
	005	17	0.20	121	97	65	315	<0.10	143	6.4	99	12.4	10.2	6.3	4.2	2.1	2	86	188	
Group 2 ER176 88.1 ug/kg IV	021	14	0.18	148	87	46	369	<0.10	142	6.4	101	12.2	11.5	5.6	3.7	1.9	2	71	142	
	022	16	0.20	114	83	49	432	<0.10	146	5.9	99	12.6	10.9	6.4	4.3	2.1	2	89	268	
	023	15	0.21	119	88	46	323	<0.10	144	6.8	98	12.6	11.7	6.2	4.1	2.1	2	118	109	
	024	12	0.21	132	87	51	449	<0.10	142	6.9	98	12.3	10.8	6.2	4.0	2.2	2	107	159	
	025	15	0.17	127	85	59	407	<0.10	143	6.6	97	12.1	10.0	6.3	4.2	2.1	2	107	136	

na = Not Applicable

Note: Any results reported < or > value indicates outside linearity limit.

Note: Hemolysis may affect the following results: Glucose, Potassium, Phosphorus, and Liver enzymes.

Sample characteristics:

1+ hemolysis: #023

Trace hemolysis: #001-005, 021, 022, 024, 025

Result obtained by repeat analysis (Ran in decreased volume mode, results automatically calculated by analyzer)

ALP: #024

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

INDIVIDUAL CLINICAL CHEMISTRY DATA

SRI Study No. M038-13

INSTRUMENT USED			Cobas c-501		INTERVAL			Day 15		SEX			Male							
ANALYSIS PERFORMED BY			RR		REVIEWED BY			NC		SPECIES			Rat (SD)							
Group	Animal ID	BUN (mg/dL)	CRE (mg/dL)	GLU (mg/dL)	AST (U/L)	ALT (U/L)	ALP (U/L)	TBI (mg/dL)	SOD (mEq/L)	POT (mEq/L)	CHL (mEq/L)	CAL (mg/dL)	PHO (mg/dL)	TPR (g/dL)	ALB (g/dL)	GLO (g/dL)	AGR	CHO (mg/dL)	TRI (mg/dL)	
Group 1 Vehicle 0 ug/kg IV	006	16	0.21	115	79	46	329	<0.10	143	5.8	98	11.7	8.7	6.4	4.4	2.0	2	72	189	
	007	15	0.26	135	84	50	272	<0.10	143	7.2	96	12.2	9.4	6.8	4.1	2.7	2	96	221	
	008	15	0.27	130	89	50	274	<0.10	146	4.9	98	11.6	7.4	6.9	4.5	2.4	2	77	125	
	009	15	0.28	120	68	43	217	<0.10	144	6.1	98	11.6	8.2	6.4	4.2	2.2	2	75	195	
	010	17	0.22	127	83	59	263	<0.10	144	6.4	98	12.1	8.6	6.6	4.5	2.1	2	87	208	
Group 2 ER176 88.1 ug/kg IV	026	16	0.26	129	70	63	234	<0.10	145	5.9	98	12.1	9.0	6.2	4.0	2.2	2	85	136	
	027	17	0.31	225	88	60	291	<0.10	144	4.2	99	12.7	8.6	6.6	4.3	2.3	2	74	150	
	028	15	0.25	196	86	60	277	<0.10	145	6.0	100	13.1	9.7	6.4	4.3	2.1	2	96	174	
	029	15	0.21	120	70	54	220	<0.10	144	6.3	98	12.2	8.7	6.4	4.0	2.4	2	106	278	
	030	14	0.23	127	64	44	290	<0.10	143	6.1	99	11.8	9.2	6.1	4.2	1.9	2	76	213	

na = Not Applicable

Note: Any results reported < or > value indicates outside linearity limit.

Note: Hemolysis may affect the following results: Glucose, Potassium, Phosphorus, and Liver enzymes.

Sample characteristics:

Trace hemolysis: #007

Result obtained by repeat analysis:

TRI: #008

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

INDIVIDUAL CLINICAL CHEMISTRY DATA

SRI Study No. M038-13

INSTRUMENT USED			Cobas c-501		INTERVAL			Day 3		SEX			Female							
ANALYSIS PERFORMED BY			DV		REVIEWED BY			NC		SPECIES			Rat (SD)							
Group	Animal ID	BUN (mg/dL)	CRE (mg/dL)	GLU (mg/dL)	AST (U/L)	ALT (U/L)	ALP (U/L)	TBI (mg/dL)	SOD (mEq/L)	POT (mEq/L)	CHL (mEq/L)	CAL (mg/dL)	PHO (mg/dL)	TPR (g/dL)	ALB (g/dL)	GLO (g/dL)	AGR	CHO (mg/dL)	TRI (mg/dL)	
Group 1 Vehicle 0 ug/kg IV	011	19	0.25	189	69	32	257	<0.10	144	4.7	103	12.8	11.9	6.2	4.0	2.2	2	87	112	
	012	13	0.20	120	78	42	223	<0.10	144	6.4	100	11.8	11.5	6.4	4.5	1.9	2	102	50	
	013	17	0.26	176	92	47	226	<0.10	142	5.2	100	12.8	12.9	6.3	4.5	1.8	3	95	49	
	014	17	0.19	120	89	47	310	<0.10	144	5.6	99	12.5	11.0	6.3	4.4	1.9	2	87	61	
	015	16	0.24	118	80	42	245	<0.10	143	6.3	100	12.5	10.6	6.8	4.9	1.9	3	112	52	
Group 2 ER176 88.1 ug/kg IV	031	17	0.26	160	84	40	156	<0.10	142	4.7	100	11.8	10.8	6.5	4.8	1.7	3	99	106	
	032	17	0.24	113	83	40	214	<0.10	144	6.0	99	12.0	11.4	6.5	4.7	1.8	3	90	78	
	033	18	0.18	128	72	41	279	<0.10	143	5.6	97	13.1	10.1	6.7	4.8	1.9	3	116	126	
	034	16	0.20	125	64	40	171	<0.10	142	5.9	97	13.1	11.6	6.3	4.4	1.9	2	109	71	
	035	12	0.26	212	76	38	182	<0.10	143	4.2	101	12.9	11.1	6.8	4.9	1.9	3	88	70	

na = Not Applicable

Note: Any results reported < or > value indicates outside linearity limit.

Note: Hemolysis may affect the following results: Glucose, Potassium, Phosphorus, and Liver enzymes.

Sample characteristics:

1+ hemolysis: #013, 014, 032

Trace hemolysis: #011, 012, 015, 031, 033-035

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

INDIVIDUAL CLINICAL CHEMISTRY DATA

SRI Study No. M038-13

INSTRUMENT USED			Cobas c-501		INTERVAL			Day 15		SEX			Female							
ANALYSIS PERFORMED BY			RR		REVIEWED BY			NC		SPECIES			Rat (SD)							
Group	Animal ID	BUN (mg/dL)	CRE (mg/dL)	GLU (mg/dL)	AST (U/L)	ALT (U/L)	ALP (U/L)	TBI (mg/dL)	SOD (mEq/L)	POT (mEq/L)	CHL (mEq/L)	CAL (mg/dL)	PHO (mg/dL)	TPR (g/dL)	ALB (g/dL)	GLO (g/dL)	AGR	CHO (mg/dL)	TRI (mg/dL)	
Group 1 Vehicle 0 ug/kg IV	016	18	0.29	131	82	56	213	<0.10	144	5.5	101	11.5	7.3	6.3	4.5	1.8	3	91	34	
	017	18	0.23	136	62	40	161	<0.10	142	5.7	97	12.2	7.9	6.6	4.7	1.9	2	105	105	
	018	18	0.28	118	80	48	172	<0.10	144	6.1	98	12.4	7.3	7.0	4.7	2.3	2	114	171	
	019	24	0.30	133	69	44	145	<0.10	144	5.5	100	12.2	8.0	6.3	4.3	2.0	2	93	102	
	020	22	0.27	114	84	46	196	<0.10	143	6.1	99	12.3	7.2	7.0	4.8	2.2	2	96	253	
Group 2 ER176 88.1 ug/kg IV	036	26	0.37	127	68	39	169	<0.10	144	5.7	98	12.2	8.4	6.9	5.0	1.9	3	88	109	
	037	22	0.28	155	74	37	233	<0.10	143	4.7	101	11.6	8.9	6.0	4.2	1.8	2	83	53	
	038	16	0.25	146	71	41	168	<0.10	145	5.7	101	12.5	9.3	6.2	4.4	1.8	2	106	34	
	039	19	0.27	127	74	54	302	<0.10	145	5.5	99	12.0	9.5	6.0	4.1	1.9	2	90	72	
	040	18	0.27	124	75	44	198	<0.10	146	5.5	100	12.3	7.8	6.8	4.5	2.3	2	107	73	

na = Not Applicable

Note: Any results reported < or > value indicates outside linearity limit.

Result obtained by repeat analysis:

SOD, POT, CHL: #037

ALP: #020

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Appendix G

INDIVIDUAL NECROPSY OBSERVATIONS

Individual Necropsy Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Group: 1 Dose: Group 1 0 Sex: Male

Animal Ref.	Mode Of Death	Death Day (Week)	Observation(s)
001	Main Sacrifice	3 (1)	No Visible Lesions
002	Main Sacrifice	3 (1)	No Visible Lesions
003	Main Sacrifice	3 (1)	No Visible Lesions
004	Main Sacrifice	3 (1)	No Visible Lesions
005	Main Sacrifice	3 (1)	No Visible Lesions
006	Recovery Sacrifice	15 (3)	No Visible Lesions
007	Recovery Sacrifice	15 (3)	No Visible Lesions
008	Recovery Sacrifice	15 (3)	SALIVARY GLAND, MANDIBULAR; Discolored; red Any remaining protocol required tissues, which have been examined, have no visible lesions
009	Recovery Sacrifice	15 (3)	No Visible Lesions
010	Recovery Sacrifice	15 (3)	No Visible Lesions

Individual Necropsy Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Group: 1 Dose: Group 1 0 Sex: Female

Animal Ref.	Mode Of Death	Death Day (Week)	Observation(s)
011	Main Sacrifice	3 (1)	No Visible Lesions
012	Main Sacrifice	3 (1)	No Visible Lesions
013	Main Sacrifice	3 (1)	No Visible Lesions
014	Main Sacrifice	3 (1)	No Visible Lesions
015	Main Sacrifice	3 (1)	No Visible Lesions
016	Recovery Sacrifice	15 (3)	No Visible Lesions
017	Recovery Sacrifice	15 (3)	No Visible Lesions
018	Recovery Sacrifice	15 (3)	No Visible Lesions
019	Recovery Sacrifice	15 (3)	No Visible Lesions
020	Recovery Sacrifice	15 (3)	No Visible Lesions

Individual Necropsy Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Group: 2 Dose: Group 2 88.1 Sex: Male

Animal Ref.	Mode Of Death	Death Day (Week)	Observation(s)
021	Main Sacrifice	3 (1)	No Visible Lesions
022	Main Sacrifice	3 (1)	LYMPH NODE, MANDIBULAR; Enlarged (TGL) Any remaining protocol required tissues, which have been examined, have no visible lesions
023	Main Sacrifice	3 (1)	No Visible Lesions
024	Main Sacrifice	3 (1)	LUNGS WITH BRONCHI; Discolored; dark Any remaining protocol required tissues, which have been examined, have no visible lesions
025	Main Sacrifice	3 (1)	No Visible Lesions
026	Recovery Sacrifice	15 (3)	No Visible Lesions
027	Recovery Sacrifice	15 (3)	No Visible Lesions
028	Recovery Sacrifice	15 (3)	No Visible Lesions
029	Recovery Sacrifice	15 (3)	LUNGS WITH BRONCHI; Mottled Any remaining protocol required tissues, which have been examined, have no visible lesions
030	Recovery Sacrifice	15 (3)	No Visible Lesions

Individual Necropsy Observations

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Group: 2 Dose: Group 2 88.1 Sex: Female

Animal Ref.	Mode Of Death	Death Day (Week)	Observation(s)
031	Main Sacrifice	3 (1)	No Visible Lesions
032	Main Sacrifice	3 (1)	No Visible Lesions
033	Main Sacrifice	3 (1)	No Visible Lesions
034	Main Sacrifice	3 (1)	No Visible Lesions
035	Main Sacrifice	3 (1)	No Visible Lesions
036	Recovery Sacrifice	15 (3)	No Visible Lesions
037	Recovery Sacrifice	15 (3)	No Visible Lesions
038	Recovery Sacrifice	15 (3)	No Visible Lesions
039	Recovery Sacrifice	15 (3)	No Visible Lesions
040	Recovery Sacrifice	15 (3)	No Visible Lesions

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Appendix H

INDIVIDUAL ORGAN WEIGHTS

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Terminal Body Wt. (g)	Adrenal Glands Wt (g)	Brain Weight (g)	Heart Weight (g)	Kidneys Weight (g)	Liver Weight (g)	Ovaries Weight (g)
	-	3	3	3	3	3	3
001	304	0.043	1.810	0.982	2.220	12.878	-
002	289	0.049	2.008	1.076	2.243	12.196	-
003	288	0.049	1.926	1.090	2.268	12.068	-
004	274	0.050	1.902	1.041	2.171	11.449	-
005	285	0.020	1.963	0.968	2.231	11.850	-
Mean	288.0	0.0422	1.9218	1.0314	2.2266	12.0882	-
SD	10.7	0.0127	0.0742	0.0547	0.0358	0.5247	-
N	5	5	5	5	5	5	-

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Spleen Weight (g)	Testes Weight (g)	Thymus Weight (g)	Adrenal/Body weight (%)	Brain/Body weight (%)	Heart/Body weight (%)	Kidney/Body weight (%)
	3	3	3	3	3	3	3
001	0.701	2.646	0.702	0.014	0.595	0.323	0.730
002	0.769	2.568	0.585	0.017	0.695	0.372	0.776
003	0.806	2.860	0.824	0.017	0.669	0.378	0.788
004	0.593	2.509	0.741	0.018	0.694	0.380	0.792
005	0.624	2.684	0.642	0.007	0.689	0.340	0.783
Mean	0.6986	2.6534	0.6988	0.0147	0.6684	0.3587	0.7738
SD	0.0911	0.1340	0.0917	0.0045	0.0421	0.0258	0.0251
N	5	5	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Liver/Body weight (%)	Ovaries/Body weight (%)	Spleen/Body weight (%)	Testes/Body weight (%)	Thymus/Body weight (%)	Adrenal/ Brain (%)	Heart/ Brain (%)
	3	3	3	3	3	3	3
001	4.236	-	0.231	0.870	0.231	2.376	54.254
002	4.220	-	0.266	0.889	0.202	2.440	53.586
003	4.190	-	0.280	0.993	0.286	2.544	56.594
004	4.178	-	0.216	0.916	0.270	2.629	54.732
005	4.158	-	0.219	0.942	0.225	1.019	49.312
Mean	4.1966	-	0.2424	0.9219	0.2430	2.2015	53.6956
SD	0.0316	-	0.0288	0.0481	0.0343	0.6682	2.6931
N	5	-	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Kidneys/ Brain (%)	Liver/ Brain (%)	Ovaries/ Brain (%)	Spleen/ Brain (%)	Testes/ Brain (%)	Thymus/ Brain (%)
	3	3	3	3	3	3
001	122.652	711.492	-	38.729	146.188	38.785
002	111.703	607.371	-	38.297	127.888	29.133
003	117.757	626.584	-	41.848	148.494	42.783
004	114.143	601.945	-	31.178	131.914	38.959
005	113.653	603.668	-	31.788	136.729	32.705
Mean	115.9815	630.2118	-	36.3681	138.2428	36.4730
SD	4.3230	46.4889	-	4.6703	8.9131	5.4636
N	5	5	-	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Terminal Body Wt. (g)	Adrenal Glands Wt (g)	Brain Weight (g)	Heart Weight (g)	Kidneys Weight (g)	Liver Weight (g)	Ovaries Weight (g)
	-	3	3	3	3	3	3
021	301	0.045	2.051	1.160	2.240	11.506	-
022	281	0.044	1.790	1.052	2.167	12.286	-
023	290	0.036	1.866	1.118	2.541	11.802	-
024	305	0.044	2.021	0.984	2.554	14.101	-
025	295	0.044	1.656	1.060	2.151	11.619	-
Mean	294.4	0.0426	1.8768	1.0748	2.3306	12.2628	-
SD	9.4	0.0037	0.1640	0.0673	0.2009	1.0699	-
N	5	5	5	5	5	5	-

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Spleen Weight (g)	Testes Weight (g)	Thymus Weight (g)	Adrenal/Body weight (%)	Brain/Body weight (%)	Heart/Body weight (%)	Kidney/Body weight (%)
	3	3	3	3	3	3	3
021	0.643	2.483	0.674	0.015	0.681	0.385	0.744
022	0.638	3.054	0.786	0.016	0.637	0.374	0.771
023	0.751	2.768	0.797	0.012	0.643	0.386	0.876
024	0.376	3.112	0.709	0.014	0.663	0.323	0.837
025	0.845	2.498	0.522	0.015	0.561	0.359	0.729
Mean	0.6506	2.7830	0.6976	0.0145	0.6372	0.3654	0.7916
SD	0.1757	0.2971	0.1109	0.0012	0.0458	0.0262	0.0629
N	5	5	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Liver/Body weight (%)	Ovaries/Body weight (%)	Spleen/Body weight (%)	Testes/Body weight (%)	Thymus/Body weight (%)	Adrenal/ Brain (%)	Heart/ Brain (%)
	3	3	3	3	3	3	3
021	3.823	-	0.214	0.825	0.224	2.194	56.558
022	4.372	-	0.227	1.087	0.280	2.458	58.771
023	4.070	-	0.259	0.954	0.275	1.929	59.914
024	4.623	-	0.123	1.020	0.232	2.177	48.689
025	3.939	-	0.286	0.847	0.177	2.657	64.010
Mean	4.1653	-	0.2219	0.9467	0.2376	2.2831	57.5883
SD	0.3281	-	0.0620	0.1117	0.0420	0.2805	5.6636
N	5	-	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Kidneys/ Brain (%)	Liver/ Brain (%)	Ovaries/ Brain (%)	Spleen/ Brain (%)	Testes/ Brain (%)	Thymus/ Brain (%)
	3	3	3	3	3	3
021	109.215	560.995	-	31.351	121.063	32.862
022	121.061	686.369	-	35.642	170.615	43.911
023	136.174	632.476	-	40.247	148.339	42.712
024	126.373	697.724	-	18.605	153.983	35.082
025	129.891	701.630	-	51.027	150.845	31.522
Mean	124.5429	655.8387	-	35.3742	148.9689	37.2175
SD	10.1771	59.8426	-	11.8976	17.8629	5.7218
N	5	5	-	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Terminal Body Wt. (g)	Adrenal Glands Wt (g)	Brain Weight (g)	Heart Weight (g)	Kidneys Weight (g)	Liver Weight (g)	Ovaries Weight (g)
	-	3	3	3	3	3	3
011	193	0.054	1.827	0.822	1.780	8.231	0.082
012	190	0.065	1.820	0.821	1.627	8.884	0.078
013	192	0.049	1.910	0.669	1.644	9.049	0.116
014	193	0.058	1.897	0.736	1.571	8.823	0.754
015	190	0.044	1.788	0.821	1.582	8.460	0.057
Mean	191.6	0.0540	1.8484	0.7738	1.6408	8.6894	0.2174
SD	1.5	0.0081	0.0526	0.0693	0.0835	0.3346	0.3007
N	5	5	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Spleen Weight (g)	Testes Weight (g)	Thymus Weight (g)	Adrenal/Body weight (%)	Brain/Body weight (%)	Heart/Body weight (%)	Kidney/Body weight (%)
	3	3	3	3	3	3	3
011	0.497	-	0.701	0.028	0.947	0.426	0.922
012	0.546	-	0.484	0.034	0.958	0.432	0.856
013	0.537	-	0.598	0.026	0.995	0.348	0.856
014	0.464	-	0.596	0.030	0.983	0.381	0.814
015	0.382	-	0.627	0.023	0.941	0.432	0.833
Mean	0.4852	-	0.6012	0.0282	0.9647	0.4040	0.8563
SD	0.0664	-	0.0781	0.0042	0.0233	0.0376	0.0409
N	5	-	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Liver/Body weight (%)	Ovaries/Body weight (%)	Spleen/Body weight (%)	Testes/Body weight (%)	Thymus/Body weight (%)	Adrenal/ Brain (%)	Heart/ Brain (%)
	3	3	3	3	3	3	3
011	4.265	0.042	0.258	-	0.363	2.956	44.992
012	4.676	0.041	0.287	-	0.255	3.571	45.110
013	4.713	0.060	0.280	-	0.311	2.565	35.026
014	4.572	0.391	0.240	-	0.309	3.057	38.798
015	4.453	0.030	0.201	-	0.330	2.461	45.917
Mean	4.5355	0.1129	0.2532	-	0.3136	2.9222	41.9686
SD	0.1821	0.1556	0.0345	-	0.0394	0.4419	4.8179
N	5	5	5	-	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Kidneys/ Brain (%)	Liver/ Brain (%)	Ovaries/ Brain (%)	Spleen/ Brain (%)	Testes/ Brain (%)	Thymus/ Brain (%)
	3	3	3	3	3	3
011	97.427	450.520	4.488	27.203	-	38.369
012	89.396	488.132	4.286	30.000	-	26.593
013	86.073	473.770	6.073	28.115	-	31.309
014	82.815	465.103	39.747	24.460	-	31.418
015	88.479	473.154	3.188	21.365	-	35.067
Mean	88.8380	470.1357	11.5564	26.2285	-	32.5513
SD	5.4346	13.7503	15.7926	3.3734	-	4.4300
N	5	5	5	5	-	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Terminal Body Wt. (g)	Adrenal Glands Wt (g)	Brain Weight (g)	Heart Weight (g)	Kidneys Weight (g)	Liver Weight (g)	Ovaries Weight (g)
	-	3	3	3	3	3	3
031	181	0.040	1.770	0.703	1.617	8.515	0.085
032	187	0.049	1.850	0.765	1.672	8.486	0.060
033	201	0.042	1.730	0.847	1.862	10.332	0.074
034	193	0.039	1.780	0.891	1.713	9.110	0.091
035	175	0.044	1.848	0.941	1.577	7.801	0.075
Mean	187.4	0.0428	1.7956	0.8294	1.6882	8.8488	0.0770
SD	10.1	0.0040	0.0522	0.0958	0.1101	0.9499	0.0119
N	5	5	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Spleen Weight (g)	Testes Weight (g)	Thymus Weight (g)	Adrenal/Body weight (%)	Brain/Body weight (%)	Heart/Body weight (%)	Kidney/Body weight (%)
	3	3	3	3	3	3	3
031	0.450	-	0.452	0.022	0.978	0.388	0.893
032	0.481	-	0.510	0.026	0.989	0.409	0.894
033	0.511	-	0.651	0.021	0.861	0.421	0.926
034	0.572	-	0.672	0.020	0.922	0.462	0.888
035	0.579	-	0.556	0.025	1.056	0.538	0.901
Mean	0.5186	-	0.5682	0.0229	0.9612	0.4437	0.9005
SD	0.0563	-	0.0931	0.0026	0.0736	0.0590	0.0152
N	5	-	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Liver/Body weight (%)	Ovaries/Body weight (%)	Spleen/Body weight (%)	Testes/Body weight (%)	Thymus/Body weight (%)	Adrenal/ Brain (%)	Heart/ Brain (%)
	3	3	3	3	3	3	3
	031	4.704	0.047	0.249	-	0.250	2.260
	032	4.538	0.032	0.257	-	0.273	2.649
	033	5.140	0.037	0.254	-	0.324	2.428
	034	4.720	0.047	0.296	-	0.348	2.191
	035	4.458	0.043	0.331	-	0.318	2.381
Mean		4.7121	0.0412	0.2775	-	0.3024	2.3816
SD		0.2639	0.0066	0.0353	-	0.0401	0.1765
N		5	5	5	-	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Kidneys/ Brain (%)	Liver/ Brain (%)	Ovaries/ Brain (%)	Spleen/ Brain (%)	Testes/ Brain (%)	Thymus/ Brain (%)
	3	3	3	3	3	3
031	91.356	481.073	4.802	25.424	-	25.537
032	90.378	458.703	3.243	26.000	-	27.568
033	107.630	597.225	4.277	29.538	-	37.630
034	96.236	511.798	5.112	32.135	-	37.753
035	85.335	422.132	4.058	31.331	-	30.087
Mean	94.1872	494.1863	4.2988	28.8855	-	31.7147
SD	8.4526	66.2384	0.7225	3.0526	-	5.6892
N	5	5	5	5	-	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Terminal Body Wt. (g)	Adrenal Glands Wt (g)	Brain Weight (g)	Heart Weight (g)	Kidneys Weight (g)	Liver Weight (g)	Ovaries Weight (g)
	-	15	15	15	15	15	15
006	358	0.057	2.033	1.271	2.836	14.138	-
007	373	0.036	1.961	1.362	2.763	14.126	-
008	319	0.045	2.026	1.176	2.538	10.971	-
009	373	0.044	2.066	1.151	2.575	15.664	-
010	315	0.058	1.887	1.032	2.478	11.692	-
Mean	347.6	0.0480	1.9946	1.1984	2.6380	13.3182	-
SD	28.6	0.0094	0.0712	0.1250	0.1536	1.9353	-
N	5	5	5	5	5	5	-

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Spleen Weight (g)	Testes Weight (g)	Thymus Weight (g)	Adrenal/Body weight (%)	Brain/Body weight (%)	Heart/Body weight (%)	Kidney/Body weight (%)
	15	15	15	15	15	15	15
006	0.712	3.269	0.441	0.016	0.568	0.355	0.792
007	0.713	3.223	0.572	0.010	0.526	0.365	0.741
008	0.559	3.064	0.348	0.014	0.635	0.369	0.796
009	0.742	3.116	0.733	0.012	0.554	0.309	0.690
010	0.514	2.993	0.430	0.018	0.599	0.328	0.787
Mean	0.6480	3.1330	0.5048	0.0140	0.5763	0.3450	0.7611
SD	0.1037	0.1132	0.1507	0.0034	0.0421	0.0260	0.0454
N	5	5	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Liver/Body weight (%)	Ovaries/Body weight (%)	Spleen/Body weight (%)	Testes/Body weight (%)	Thymus/Body weight (%)	Adrenal/ Brain (%)	Heart/ Brain (%)
	15	15	15	15	15	15	15
006	3.949	-	0.199	0.913	0.123	2.804	62.518
007	3.787	-	0.191	0.864	0.153	1.836	69.454
008	3.439	-	0.175	0.961	0.109	2.221	58.045
009	4.199	-	0.199	0.835	0.197	2.130	55.712
010	3.712	-	0.163	0.950	0.137	3.074	54.690
Mean	3.8173	-	0.1855	0.9047	0.1437	2.4128	60.0839
SD	0.2822	-	0.0158	0.0541	0.0337	0.5097	6.0436
N	5	-	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Kidneys/ Brain (%)	Liver/ Brain (%)	Ovaries/ Brain (%)	Spleen/ Brain (%)	Testes/ Brain (%)	Thymus/ Brain (%)
	15	15	15	15	15	15
006	139.498	695.425	-	35.022	160.797	21.692
007	140.898	720.347	-	36.359	164.355	29.169
008	125.271	541.510	-	27.591	151.234	17.177
009	124.637	758.180	-	35.915	150.823	35.479
010	131.320	619.608	-	27.239	158.612	22.787
Mean	132.3248	667.0141	-	32.4253	157.1640	25.2609
SD	7.6618	86.5467	-	4.6005	5.9661	7.1396
N	5	5	-	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Terminal Body Wt. (g)	Adrenal Glands Wt (g)	Brain Weight (g)	Heart Weight (g)	Kidneys Weight (g)	Liver Weight (g)	Ovaries Weight (g)
	-	15	15	15	15	15	15
026	351	0.045	1.886	1.135	2.570	13.136	-
027	334	0.044	1.964	1.148	2.384	12.630	-
028	365	0.058	1.873	1.163	2.716	12.973	-
029	364	0.057	2.074	1.293	2.741	14.712	-
030	383	0.051	1.972	1.265	2.802	14.621	-
Mean	359.4	0.0510	1.9538	1.2008	2.6426	13.6144	-
SD	18.2	0.0065	0.0806	0.0727	0.1678	0.9782	-
N	5	5	5	5	5	5	-

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Spleen Weight (g)	Testes Weight (g)	Thymus Weight (g)	Adrenal/Body weight (%)	Brain/Body weight (%)	Heart/Body weight (%)	Kidney/Body weight (%)
	15	15	15	15	15	15	15
026	0.729	3.358	0.486	0.013	0.537	0.323	0.732
027	0.824	3.287	0.516	0.013	0.588	0.344	0.714
028	0.541	3.169	0.610	0.016	0.513	0.319	0.744
029	0.740	3.089	0.839	0.016	0.570	0.355	0.753
030	0.767	3.357	0.499	0.013	0.515	0.330	0.732
Mean	0.7202	3.2520	0.5900	0.0142	0.5446	0.3342	0.7349
SD	0.1067	0.1193	0.1475	0.0015	0.0333	0.0151	0.0148
N	5	5	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Liver/Body weight (%)	Ovaries/Body weight (%)	Spleen/Body weight (%)	Testes/Body weight (%)	Thymus/Body weight (%)	Adrenal/ Brain (%)	Heart/ Brain (%)
	15	15	15	15	15	15	15
026	3.742	-	0.208	0.957	0.138	2.386	60.180
027	3.781	-	0.247	0.984	0.154	2.240	58.452
028	3.554	-	0.148	0.868	0.167	3.097	62.093
029	4.042	-	0.203	0.849	0.230	2.748	62.343
030	3.817	-	0.200	0.877	0.130	2.586	64.148
Mean	3.7875	-	0.2012	0.9068	0.1642	2.6115	61.4433
SD	0.1747	-	0.0351	0.0597	0.0397	0.3329	2.1846
N	5	-	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Male Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Kidneys/ Brain (%)	Liver/ Brain (%)	Ovaries/ Brain (%)	Spleen/ Brain (%)	Testes/ Brain (%)	Thymus/ Brain (%)
	15	15	15	15	15	15
026	136.267	696.501	-	38.653	178.049	25.769
027	121.385	643.075	-	41.955	167.363	26.273
028	145.008	692.632	-	28.884	169.194	32.568
029	132.160	709.354	-	35.680	148.939	40.453
030	142.089	741.430	-	38.895	170.233	25.304
Mean	135.3819	696.5984	-	36.8134	166.7555	30.0735
SD	9.2834	35.5423	-	4.9576	10.7630	6.5131
N	5	5	-	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Terminal Body Wt. (g)	Adrenal Glands Wt (g)	Brain Weight (g)	Heart Weight (g)	Kidneys Weight (g)	Liver Weight (g)	Ovaries Weight (g)
	-	15	15	15	15	15	15
016	205	0.064	1.919	0.787	1.607	7.717	0.106
017	233	0.064	1.884	0.743	1.799	9.589	0.090
018	225	0.058	1.869	0.775	1.690	8.859	0.081
019	252	0.083	1.925	0.894	2.018	10.872	0.113
020	228	0.059	1.899	0.826	1.759	10.057	0.081
Mean	228.6	0.0656	1.8992	0.8050	1.7746	9.4188	0.0942
SD	16.9	0.0101	0.0235	0.0579	0.1544	1.1997	0.0147
N	5	5	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Spleen Weight (g)	Testes Weight (g)	Thymus Weight (g)	Adrenal/Body weight (%)	Brain/Body weight (%)	Heart/Body weight (%)	Kidney/Body weight (%)
	15	15	15	15	15	15	15
016	0.466	-	0.460	0.031	0.936	0.384	0.784
017	0.541	-	0.609	0.027	0.809	0.319	0.772
018	0.483	-	0.486	0.026	0.831	0.344	0.751
019	0.667	-	0.660	0.033	0.764	0.355	0.801
020	0.512	-	0.518	0.026	0.833	0.362	0.771
Mean	0.5338	-	0.5466	0.0287	0.8344	0.3529	0.7759
SD	0.0798	-	0.0848	0.0033	0.0632	0.0239	0.0182
N	5	-	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Liver/Body weight (%)	Ovaries/Body weight (%)	Spleen/Body weight (%)	Testes/Body weight (%)	Thymus/Body weight (%)	Adrenal/ Brain (%)	Heart/ Brain (%)
	15	15	15	15	15	15	15
016	3.764	0.052	0.227	-	0.224	3.335	41.011
017	4.115	0.039	0.232	-	0.261	3.397	39.437
018	3.937	0.036	0.215	-	0.216	3.103	41.466
019	4.314	0.045	0.265	-	0.262	4.312	46.442
020	4.411	0.036	0.225	-	0.227	3.107	43.497
Mean	4.1085	0.0413	0.2327	-	0.2382	3.4508	42.3705
SD	0.2653	0.0069	0.0190	-	0.0218	0.4991	2.6977
N	5	5	5	-	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 1 0 ug/kg IV	Kidneys/ Brain (%)	Liver/ Brain (%)	Ovaries/ Brain (%)	Spleen/ Brain (%)	Testes/ Brain (%)	Thymus/ Brain (%)
	15	15	15	15	15	15
016	83.742	402.137	5.524	24.283	-	23.971
017	95.488	508.970	4.777	28.715	-	32.325
018	90.423	473.997	4.334	25.843	-	26.003
019	104.831	564.779	5.870	34.649	-	34.286
020	92.628	529.595	4.265	26.962	-	27.278
Mean	93.4223	495.8955	4.9540	28.0905	-	28.7724
SD	7.7100	61.8907	0.7166	4.0072	-	4.3582
N	5	5	5	5	-	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Terminal Body Wt. (g)	Adrenal Glands Wt (g)	Brain Weight (g)	Heart Weight (g)	Kidneys Weight (g)	Liver Weight (g)	Ovaries Weight (g)
	-	15	15	15	15	15	15
036	228	0.074	1.868	1.114	1.882	9.121	0.072
037	221	0.041	1.906	0.822	1.716	7.822	0.077
038	225	0.064	1.864	0.945	1.792	9.684	0.106
039	232	0.047	1.924	0.866	1.681	9.879	0.084
040	218	0.061	1.957	0.847	1.689	8.663	0.106
Mean	224.8	0.0574	1.9038	0.9188	1.7520	9.0338	0.0890
SD	5.5	0.0133	0.0391	0.1184	0.0849	0.8293	0.0161
N	5	5	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Spleen Weight (g)	Testes Weight (g)	Thymus Weight (g)	Adrenal/Body weight (%)	Brain/Body weight (%)	Heart/Body weight (%)	Kidney/Body weight (%)
	15	15	15	15	15	15	15
036	0.633	-	0.584	0.032	0.819	0.489	0.825
037	0.443	-	0.544	0.019	0.862	0.372	0.776
038	0.596	-	0.467	0.028	0.828	0.420	0.796
039	0.564	-	0.532	0.020	0.829	0.373	0.725
040	0.614	-	0.665	0.028	0.898	0.389	0.775
Mean	0.5700	-	0.5584	0.0255	0.8474	0.4085	0.7795
SD	0.0754	-	0.0729	0.0059	0.0325	0.0488	0.0369
N	5	-	5	5	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Liver/Body weight (%)	Ovaries/Body weight (%)	Spleen/Body weight (%)	Testes/Body weight (%)	Thymus/Body weight (%)	Adrenal/ Brain (%)	Heart/ Brain (%)
	15	15	15	15	15	15	15
	036	4.000	0.032	0.278	-	0.256	3.961
037	3.539	0.035	0.200	-	0.246	2.151	43.127
038	4.304	0.047	0.265	-	0.208	3.433	50.697
039	4.258	0.036	0.243	-	0.229	2.443	45.010
040	3.974	0.049	0.282	-	0.305	3.117	43.281
Mean	4.0152	0.0397	0.2535	-	0.2488	3.0212	48.3503
SD	0.3045	0.0077	0.0333	-	0.0364	0.7340	7.0181
N	5	5	5	-	5	5	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Sex: Female Day(s) Relative to Start Date

Group 2 88.1 ug/kg IV	Kidneys/ Brain (%)	Liver/ Brain (%)	Ovaries/ Brain (%)	Spleen/ Brain (%)	Testes/ Brain (%)	Thymus/ Brain (%)
	15	15	15	15	15	15
036	100.749	488.276	3.854	33.887	-	31.263
037	90.031	410.388	4.040	23.242	-	28.541
038	96.137	519.528	5.687	31.974	-	25.054
039	87.370	513.462	4.366	29.314	-	27.651
040	86.306	442.667	5.416	31.375	-	33.981
Mean	92.1188	474.8643	4.6727	29.9583	-	29.2980
SD	6.1510	47.0592	0.8285	4.0933	-	3.4311
N	5	5	5	5	-	5

Individual Organ Weights

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Key Page

General Footnotes

- Not Applicable

Group Information

<u>Short Name</u>	<u>Long Name</u>	<u>Report Headings 1-4</u>		
1	Vehicle	Group 1	0	ug/kg IV
2	ER176	Group 2	88.1	ug/kg IV

**Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13**

Appendix I

HISTOPATHOLOGY


Ken Altera, DVM, PhD, DACVP
Westpath Corporation
Veterinary Pathologist


11 Nov 2013
Date

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Appendix I-1

PATHOLOGY NARRATIVE

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

Pathology Narrative

Microscopic changes were coded by the most specific topographic and morphologic diagnosis, and SNOMED (Systematized Nomenclature of Medicine), NTP (National Toxicology Program) and TDMS (Toxicology Data Management System) terminology manuals were used as guidelines. Data were recorded in Provantis Pathology ver. 8.6.1.3. A four step grading system (minimal, mild, moderate and marked) was used to define gradable changes. Records of necropsy findings and changes found at tissue processing were available when evaluating the stained tissue sections. Histopathology data are presented as summary and individual animal tables. A codes table defines the table entries.

Sprague Dawley rats were used for this study. Study Groups 1 and 2 each consisted of 10 males and 10 females. Dosing was intravenous (IV) in the tail vein on Day 1. All rats survived until their scheduled necropsy examination was performed on Day 3 for the Main group sacrifice and Day 15 for the Recovery group sacrifice. Group 1 served as the vehicle-control group and received vehicle only at a volume of 5 ml/kg. Group 2 received ER176 (100x Human Dose) at a volume of 5 ml/kg.

No histopathologic change attributed to ER176 was observed in Group 2 rats following IV administration at either the Day 3 Main group sacrifice or the Day 15 Recovery group sacrifice. Histopathologic findings were generally similar in Groups 1 and 2, and were usually characteristic of background changes commonly seen in control rats of comparable age and gender.

Findings at the main sacrifice were present that were not attributed to ER176. Epididymal aspermia or hypospermia in 3 Group 2 males were incidental findings and reflected only the level of maturity (mature sperm not yet present in epididymal duct lumen) because spermatogenesis was normal in the testes of these rats and prostate and seminal vesicles were normal. Myocardial and epicardial inflammation were limited to Group 2 females and these changes were compatible with Spontaneous Murine Cardiomyopathy, a spontaneously occurring condition commonly seen in rats. Minor hemorrhage, inflammation, and/or vein degeneration involving tail injection veins or associated soft tissue were present in 1 male and 2 females in Group 2 and these changes were attributed to mechanical trauma of the IV injection. Increased hepatocyte mitotic activity was present in both Groups 1 and 2 males and females and did not differ meaningfully between groups.

Findings at the recovery sacrifice were present that were not attributed to ER176. Myocardial and epicardial inflammation in Groups 1 and 2 males and females were again attributed to Spontaneous Murine Cardiomyopathy. Increased hepatocytic mitotic activity was present in both Groups 1 and 2 males and a Group 1 female. Mitoses were slightly more prominent in Group 2 than in Group 1 males, but this difference was not regarded as biologically meaningful. Mild hyperplasia and hyperkeratosis of non-glandular stomach epithelium in a single Group 2 male were regarded as incidental findings.

Other minor differences in incidence, nature, and/or severity of findings did exist between vehicle-control rats and those exposed to ER176. These differences were not attributed to ER176 and were not regarded as biologically meaningful. Such findings were generally

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13

similar to those commonly encountered as incidental background findings in control rats of comparable age and gender. They were not attributed to the test compound or regarded as biologically meaningful. Hemorrhage, especially in the brain, thymus, lung, and heart, was fresh/acute and was attributed to hypoxia during the euthanasia process and/or to manipulation of organs at necropsy. Such hemorrhage is common in euthanized rats.

Some tissues scheduled for histopathologic examination were not evaluated. From the Main group, 10 scheduled tissues were not examined. From the Recovery group, 8 scheduled tissues were not examined. These represented tissues that were absent in the sections (such as male mammary glands and parathyroid glands), tissues that were not sectioned, and/or tissues that were not harvested at necropsy. These 18 unexamined tissues did not compromise the interpretation of histopathologic findings.

Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
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Appendix I-2

HISTOPATHOLOGY SUMMARY

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
ADRENAL GLANDS						
Examined	5	5			5	5
Normal	4	5			5	5
cortex; Hypertrophy; nodular, few	1	0			0	0
.... minimal	1	0			0	0
.... mild	0	0			0	0
AORTA						
Examined	5	5			5	5
Normal	5	5			5	5
BONE MARROW SMEAR, STERNUM						
CYTOLOGY						
Examined	5	5			5	5
Normal	5	5			5	5
Not Examined: No Section	0	0			0	0
BONE, FEMUR WITH FEMORO-TIBIAL JOINT						
Examined	5	5			5	5
Normal	5	5			5	5
BONE, STERNUM						
Examined	5	5			5	5
Normal	5	5			5	5
BONE, STERNUM (MARROW HISTOLOGY)						
Examined	5	5			5	5
Normal	4	5			5	5
Myelofibrosis; focal	1	0			0	0
.... mild	1	0			0	0
BRAIN (FORE-, MID-, HINDBRAIN)						
Examined	5	5			5	5
Normal	0	0			1	1
Hemorrhage; acute, multifocal	5	5			4	4
.... minimal	4	5			2	3
.... mild	1	0			2	1
ventricle; Dilation	1	3			1	0
.... mild	1	3			1	0
CERVIX						
Examined	.	.			5	5
Normal	.	.			5	5

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	Number of Animals:	
EPIDIDYMIDES						
Examined	5	5			.	.
Normal	5	2			.	.
Aspermia	0	1			.	.
.... present	0	1			.	.
duct; lumen; Debris; diffuse	0	1			.	.
.... mild	0	1			.	.
duct; lumen; Debris; few	0	1			.	.
.... minimal	0	1			.	.
duct; lumen; Hypocellularity; spermatozoal	0	2			.	.
.... mild	0	1			.	.
.... marked	0	1			.	.
ESOPHAGUS						
Examined	5	5			5	5
Normal	5	5			5	5
submucosa; Inflammation; focal	0	0			0	0
.... minimal	0	0			0	0
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL)						
Examined	5	5			5	5
Normal	4	4			1	3
periocular; Hemorrhage; acute, focal	0	1			2	0
.... mild	0	1			2	0
Inflammation; multifocal	0	0			1	0
.... minimal	0	0			1	0
periocular; Inflammation; few	0	1			0	2
.... minimal	0	1			0	2
retina; Dysplasia; few	0	0			2	0
.... minimal	0	0			2	0
.... mild	0	0			0	0
retina; Dysplasia; focal	1	0			0	0
.... minimal	1	0			0	0
retina; Dysplasia; multifocal	0	0			0	0
.... mild	0	0			0	0
HEART						
Examined	5	5			5	5

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
HEART (Continued...)						
Normal	0	0			1	1
Hemorrhage; acute, few	5	5			4	1
.... minimal	5	5			4	1
.... mild	0	0			0	0
Inflammation; few	0	0			0	1
.... minimal	0	0			0	1
Inflammation; focal	0	0			0	2
.... minimal	0	0			0	2
Inflammation; multifocal	0	0			0	0
.... mild	0	0			0	0
epicardium; Inflammation; focal	0	0			0	1
.... minimal	0	0			0	1
Epicarditis; focal	0	0			0	0
.... minimal	0	0			0	0
INJECTION SITE: TAIL, ENTIRE						
TAIL, ENTIRE : Examined	5	5			5	4
TAIL, ENTIRE : Normal	5	4			5	2
TAIL, ENTIRE : Not Examined: Lost At Necropsy	0	0			0	1
TAIL, ENTIRE : Not Examined: Not Collected	0	0			0	0
TAIL, ENTIRE : perivascular; Hemorrhage; acute, focal	0	1			0	0
.... minimal	0	1			0	0
TAIL, ENTIRE : perivascular; Inflammation; focal	0	1			0	2
.... minimal	0	1			0	1
.... mild	0	0			0	1
TAIL, ENTIRE : vein; Degeneration; focal	0	0			0	1
.... moderate	0	0			0	1
INTESTINE, CECUM						
Examined	5	5			5	5
Normal	2	0			2	3
mucosa; Congestion; multifocal	0	1			0	0
.... mild	0	1			0	0
submucosa; Congestion; few	1	2			0	2

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:	5	5	5	5	5
INTESTINE, CECUM (Continued...)						
.... mild	1	2			0	2
submucosa; Edema; diffuse	2	1			2	1
.... mild	2	1			2	1
submucosa; Edema; focal	0	0			0	0
.... mild	0	0			0	0
submucosa; Edema; multifocal	1	3			1	1
.... mild	1	3			1	1
INTESTINE, COLON						
Examined	5	4			5	5
Normal	5	4			5	5
Not Examined: No Section	0	1			0	0
submucosa; Congestion; multifocal	0	0			0	0
.... mild	0	0			0	0
submucosa; Edema; multifocal	0	0			0	0
.... mild	0	0			0	0
INTESTINE, DUODENUM						
Examined	5	5			5	5
Normal	5	5			5	5
INTESTINE, ILEUM						
Examined	5	5			5	5
Normal	5	5			5	5
INTESTINE, JEJUNUM						
Examined	5	5			5	5
Normal	5	5			5	5
INTESTINE, RECTUM						
Examined	5	5			5	5
Normal	5	4			5	5
Not Examined: No Section	0	0			0	0
submucosa; Congestion; few	0	1			0	0
.... mild	0	1			0	0
KIDNEYS						
Examined	5	5			5	5
Normal	0	1			1	0
Cast; few	0	0			0	0
.... minimal	0	0			0	0

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
KIDNEYS (Continued...)						
Fibrosis; focal	1	0			1	1
.... minimal	1	0			1	1
.... mild	0	0			0	0
Inflammation; few	1	2			2	1
.... minimal	1	1			1	1
.... mild	0	1			1	0
Inflammation; focal	0	0			0	1
.... minimal	0	0			0	1
Inflammation; multifocal	0	0			0	0
.... minimal	0	0			0	0
Mineralization; few	0	0			0	2
.... minimal	0	0			0	2
Mineralization; focal	0	1			0	1
.... minimal	0	1			0	1
epithelium; tubule; Regeneration; few	2	0			0	1
.... minimal	2	0			0	1
epithelium; tubule; Regeneration; focal	1	0			0	2
.... minimal	1	0			0	2
epithelium; tubule; Regeneration; multifocal	2	3			2	1
.... minimal	2	3			2	1
tubule; epithelium; Regeneration; multifocal	0	0			2	0
.... mild	0	0			2	0
Cyst; few	0	0			0	1
.... minimal	0	0			0	1
.... mild	0	0			0	0
Cyst; focal	0	0			1	1
.... minimal	0	0			1	1
Dilation	0	0			0	0
.... mild	0	0			0	0
LIVER						
Examined	5	5			5	5
Hematopoiesis; few	2	0			1	1
.... minimal	2	0			0	1
.... mild	0	0			1	0

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
LIVER (Continued...)						
Hematopoiesis; multifocal	0	0			0	0
.... mild	0	0			0	0
periportal; Inflammation; few	1	4			4	3
.... minimal	1	3			2	3
.... mild	0	1			2	0
periportal; Inflammation; multifocal	1	0			0	1
.... minimal	1	0			0	1
hepatocyte; Mitosis Increased; widespread	5	5			1	1
.... minimal	0	0			1	0
.... mild	1	2			0	1
.... moderate	3	2			0	0
.... marked	1	1			0	0
hepatocyte; cytoplasm; Vacuolation; diffuse	2	3			5	3
.... minimal	0	0			0	1
.... mild	1	3			2	1
.... moderate	1	0			3	1
hepatocyte; cytoplasm; Vacuolation; multifocal	3	1			0	1
.... minimal	0	0			0	0
.... mild	1	0			0	0
.... moderate	2	1			0	1
hepatocyte; cytoplasm; Fatty Infiltration; diffuse	0	0			0	1
.... minimal	0	0			0	1
hepatocyte; cytoplasm; Fatty Infiltration; multifocal	0	0			1	0
.... minimal	0	0			0	0
.... mild	0	0			1	0
hepatocyte; cytoplasm; Inclusion; eosinophilic, multifocal	0	0			0	0
.... mild	0	0			0	0
LUNGS WITH BRONCHI						
Examined	5	5			5	5
alveolus; Hemorrhage; acute, multifocal	5	5			5	5
.... minimal	0	1			3	3
.... mild	5	3			2	2
.... moderate	0	1			0	0

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:	5	5	5	5	
LUNGS WITH BRONCHI (Continued...)						
peribronchiolar; Hemorrhage; acute, few	0	2			0	0
.... minimal	0	2			0	0
peribronchiolar; Hemorrhage; acute, multifocal	0	1			0	0
.... mild	0	1			0	0
perivascular; Hemorrhage; acute, few	4	3			3	5
.... minimal	3	2			3	4
.... mild	1	1			0	1
perivascular; Hemorrhage; acute, multifocal	0	2			0	0
.... mild	0	1			0	0
.... moderate	0	1			0	0
alveolus; macrophage; Proliferation; diffuse	0	1			0	0
.... mild	0	1			0	0
alveolus; macrophage; Proliferation; few	0	0			0	0
.... minimal	0	0			0	0
alveolus; macrophage; Proliferation; multifocal	1	1			2	1
.... mild	1	1			2	1
macrophage; alveolus; Proliferation; multifocal	4	3			3	4
.... minimal	4	3			3	4
alveolus; Edema; multifocal	0	1			0	0
.... mild	0	1			0	0
perivascular; Edema; few	1	2			1	1
.... minimal	1	2			1	1
perivascular; Edema; multifocal	1	2			1	0
.... minimal	0	1			0	0
.... mild	1	1			1	0
artery; Mineralization; focal	1	0			1	0
.... minimal	1	0			1	0
peribronchiolar; Inflammation; focal	1	0			0	0
.... minimal	1	0			0	0
perivascular; Inflammation; few	1	2			1	2
.... minimal	1	2			1	2
perivascular; Inflammation; multifocal	0	1			2	0
.... mild	0	1			2	0

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
LYMPH NODE, MESENTERIC						
Examined	5	5			5	5
Normal	3	3			5	4
Hemorrhage; acute, few	2	1			0	1
.... minimal	2	1			0	1
Hemorrhage; acute, multifocal	0	1			0	0
.... minimal	0	1			0	0
LYMPH NODE, MANDIBULAR						
Examined	5	5			5	5
Hemorrhage; acute, few	0	0			1	3
.... minimal	0	0			1	3
Hemorrhage; acute, multifocal	5	4			3	0
.... minimal	2	1			0	0
.... mild	3	1			3	0
.... moderate	0	2			0	0
Plasmacytosis	5	5			5	5
.... mild	2	2			3	2
.... moderate	3	3			2	2
.... marked	0	0			0	1
Hyperplasia; lymphoid	1	1			0	0
.... moderate	1	1			0	0
MAMMARY GLANDS						
Examined	2	2			5	5
Normal	2	1			5	5
Not Examined: Not Present	3	3			0	0
perivascular; Hemorrhage; acute, few	0	1			0	0
.... mild	0	1			0	0
SKELETAL MUSCLE						
Examined	5	5			5	5
Normal	5	5			5	5
NERVE, SCIATIC						
Examined	5	5			5	5
Normal	5	5			5	5
OVARIES						
Examined	.	.			5	5
Normal	.	.			4	5

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1		Group 2		Group 1	
	0 ug/kg IV	88.1 ug/kg IV			0 ug/kg IV	88.1 ug/kg IV
Number of Animals:	5	5			5	5
OVARIES (Continued...)						
follicle; Cyst; few	.	.			1	0
.... mild	.	.			1	0
PANCREAS						
Examined	5	5			5	5
Normal	5	4			5	5
Inflammation; few	0	0			0	0
.... mild	0	0			0	0
periductal; Inflammation; few	0	0			0	0
.... minimal	0	0			0	0
periductal; Inflammation; focal	0	1			0	0
.... minimal	0	1			0	0
PARATHYROID GLAND						
Examined	5	5			4	5
Normal	5	5			4	5
Not Examined: Not Present	0	0			1	0
PITUITARY GLAND						
Examined	5	5			5	5
Normal	5	5			4	5
Cyst; few	0	0			1	0
.... minimal	0	0			1	0
Cyst; focal	0	0			0	0
.... minimal	0	0			0	0
PROSTATE GLAND						
Examined	5	5			.	.
Normal	4	4			.	.
Inflammation; multifocal	1	1			.	.
.... mild	1	1			.	.
SALIVARY GLAND, MANDIBULAR						
Examined	5	5			5	5
Normal	5	4			5	5
Hemorrhage; acute, few	0	0			0	0
.... minimal	0	0			0	0
acinar cell; cytoplasm; Inclusion; focal	0	1			0	0
.... moderate	0	1			0	0

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
SEMINAL VESICLES						
Examined	5	5			.	.
Normal	5	5			.	.
SKIN, VENTRAL ABDOMEN						
Examined	5	5			5	5
Normal	5	5			5	4
subcutaneous; Hemorrhage; acute, few	0	0			0	1
.... minimal	0	0			0	1
Acanthosis; focal	0	0			0	0
.... minimal	0	0			0	0
Hyperkeratosis; focal	0	0			0	0
.... minimal	0	0			0	0
Parakeratosis; few	0	0			0	0
.... minimal	0	0			0	0
dermis; Inflammation; few	0	0			0	0
.... minimal	0	0			0	0
SPINAL COLUMN						
Examined	4	5			5	5
Normal	4	5			5	5
SPINAL CORD, THORACOLUMBAR						
Examined	5	5			5	5
Normal	4	4			4	5
Hemorrhage; acute, few	0	1			1	0
.... minimal	0	1			1	0
Hemorrhage; acute, focal	1	0			0	0
.... minimal	1	0			0	0
SPLEEN						
Examined	5	5			5	5
Congestion	5	5			4	5
.... mild	4	5			2	4
.... moderate	1	0			2	1
Hematopoiesis	5	5			5	5
.... mild	3	0			5	5
.... moderate	2	4			0	0
.... marked	0	1			0	0

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
STOMACH, INCLUDING NONGLANDULAR						
Examined	5	5			5	5
Normal	0	0			0	0
mucosa; glandular; Hemorrhage; acute, few	0	0			0	0
.... minimal	0	0			0	0
non-glandular; epithelium; Hyperplasia; multifocal	0	1			0	0
.... mild	0	1			0	0
glandular; submucosa; Inflammation; diffuse	0	0			2	0
.... mild	0	0			2	0
submucosa; glandular; Inflammation; few	2	4			1	2
.... minimal	2	4			1	2
submucosa; glandular; Inflammation; multifocal	3	1			2	3
.... minimal	1	0			0	0
.... mild	2	1			2	3
submucosa; non-glandular; Inflammation; few	1	3			2	3
.... minimal	1	3			2	3
submucosa; non-glandular; Inflammation; multifocal	0	0			0	0
.... mild	0	0			0	0
non-glandular; epithelium; Hyperkeratosis; multifocal	0	1			0	0
.... mild	0	1			0	0
non-glandular; epithelium; Inclusion; few	0	1			0	0
.... minimal	0	1			0	0
TESTES						
Examined	5	5			.	.
Normal	4	5			.	.
seminiferous tubule; Hemorrhage; acute, few	1	0			.	.
.... minimal	1	0			.	.
THYMUS						
Examined	5	5			5	5
Normal	1	1			1	2
Hemorrhage; acute, few	2	3			4	1
.... minimal	2	3			4	1
.... mild	0	0			0	0

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
THYMUS (Continued...)						
Hemorrhage; acute, focal	0	0			0	1
.... minimal	0	0			0	1
Hemorrhage; acute, multifocal	2	1			0	1
.... minimal	2	0			0	1
.... mild	0	1			0	0
THYROID GLAND						
Examined	5	5			5	5
Normal	4	4			3	4
Cyst; ultimobranchial, few	0	0			2	1
.... minimal	0	0			1	1
.... mild	0	0			1	0
Cyst; ultimobranchial, focal	1	1			0	0
.... minimal	1	1			0	0
Inflammation; focal	0	0			0	0
.... minimal	0	0			0	0
TRACHEA						
Examined	5	5			5	5
mucosa; Hemorrhage; acute, few	0	1			0	0
.... minimal	0	1			0	0
.... mild	0	0			0	0
mucosa; Hemorrhage; acute, focal	0	0			0	0
.... mild	0	0			0	0
mucosa; Hemorrhage; acute, multifocal	0	1			0	0
.... mild	0	1			0	0
mucosa; Hemorrhage; few	0	0			1	0
.... minimal	0	0			1	0
mucosa; Inflammation; multifocal	5	5			5	5
.... minimal	0	1			0	1
.... mild	5	3			5	4
.... moderate	0	1			0	0
mucosa; glands; Dilation; multifocal	5	5			4	5
.... minimal	0	0			0	0
.... mild	2	2			2	1
.... moderate	3	3			2	4

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Main Sacrifice	Male				Female	
	Group 1		Group 2		Group 1	
	0 ug/kg IV	88.1 ug/kg IV			0 ug/kg IV	88.1 ug/kg IV
Number of Animals:	5	5			5	5
TRACHEA (Continued...)						
.... marked	0	0			0	0
URINARY BLADDER						
Examined	5	5			5	4
Normal	5	5			5	4
Not Examined: No Section	0	0			0	1
submucosa; Edema; diffuse	0	0			0	0
.... moderate	0	0			0	0
submucosa; Congestion; multifocal	0	0			0	0
.... mild	0	0			0	0
UTERUS						
Examined	.	.			5	5
Normal	.	.			4	4
Dilation	.	.			1	1
.... mild	.	.			0	1
.... moderate	.	.			0	0
.... marked	.	.			1	0
VAGINA						
Examined	.	.			5	5
Normal	.	.			5	5

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
ADRENAL GLANDS						
Examined	5	5			5	5
Normal	4	5			2	4
cortex; Hypertrophy; nodular, few	1	0			3	1
.... minimal	0	0			1	1
.... mild	1	0			2	0
AORTA						
Examined	5	5			5	5
Normal	5	5			5	5
BONE MARROW SMEAR, STERNUM						
CYTOLOGY						
Examined	5	5			5	4
Normal	5	5			5	4
Not Examined: No Section	0	0			0	1
BONE, FEMUR WITH FEMORO-TIBIAL JOINT						
Examined	5	5			5	5
Normal	5	5			5	5
BONE, STERNUM						
Examined	5	5			5	5
Normal	5	5			5	5
BONE, STERNUM (MARROW HISTOLOGY)						
Examined	5	5			5	5
Normal	5	5			5	5
Myelofibrosis; focal	0	0			0	0
.... mild	0	0			0	0
BRAIN (FORE-, MID-, HINDBRAIN)						
Examined	5	5			5	5
Normal	0	0			0	0
Hemorrhage; acute, multifocal	5	5			5	5
.... minimal	2	4			4	4
.... mild	3	1			1	1
ventricle; Dilation	0	2			3	2
.... mild	0	2			3	2
CERVIX						
Examined	.	.			5	5
Normal	.	.			5	5

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
EPIDIDYMIDES						
Examined	5	5			.	.
Normal	5	5			.	.
Aspermia	0	0			.	.
.... present	0	0			.	.
duct; lumen; Debris; diffuse	0	0			.	.
.... mild	0	0			.	.
duct; lumen; Debris; few	0	0			.	.
.... minimal	0	0			.	.
duct; lumen; Hypocellularity; spermatozoal	0	0			.	.
.... mild	0	0			.	.
.... marked	0	0			.	.
ESOPHAGUS						
Examined	5	5			5	5
Normal	5	5			4	5
submucosa; Inflammation; focal	0	0			1	0
.... minimal	0	0			1	0
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL)						
Examined	5	5			5	5
Normal	3	4			5	4
periocular; Hemorrhage; acute, focal	0	0			0	0
.... mild	0	0			0	0
Inflammation; multifocal	0	0			0	0
.... minimal	0	0			0	0
periocular; Inflammation; few	0	0			0	0
.... minimal	0	0			0	0
retina; Dysplasia; few	1	1			0	1
.... minimal	1	0			0	0
.... mild	0	1			0	1
retina; Dysplasia; focal	0	0			0	0
.... minimal	0	0			0	0
retina; Dysplasia; multifocal	1	0			0	0
.... mild	1	0			0	0
HEART						
Examined	5	5			5	5

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
HEART (Continued...)						
Normal	1	1			2	3
Hemorrhage; acute, few	4	2			2	2
.... minimal	4	2			1	2
.... mild	0	0			1	0
Inflammation; few	0	1			0	1
.... minimal	0	1			0	1
Inflammation; focal	1	0			0	0
.... minimal	1	0			0	0
Inflammation; multifocal	0	0			1	0
.... mild	0	0			1	0
epicardium; Inflammation; focal	0	0			0	0
.... minimal	0	0			0	0
Epicarditis; focal	0	1			0	0
.... minimal	0	1			0	0
INJECTION SITE: TAIL, ENTIRE						
TAIL, ENTIRE : Examined	5	5			5	4
TAIL, ENTIRE : Normal	5	5			5	4
TAIL, ENTIRE : Not Examined: Lost At Necropsy	0	0			0	0
TAIL, ENTIRE : Not Examined: Not Collected	0	0			0	1
TAIL, ENTIRE : perivascular; Hemorrhage; acute, focal	0	0			0	0
.... minimal	0	0			0	0
TAIL, ENTIRE : perivascular; Inflammation; focal	0	0			0	0
.... minimal	0	0			0	0
.... mild	0	0			0	0
TAIL, ENTIRE : vein; Degeneration; focal	0	0			0	0
.... moderate	0	0			0	0
INTESTINE, CECUM						
Examined	5	5			5	5
Normal	2	3			1	2
mucosa; Congestion; multifocal	0	1			0	0
.... mild	0	1			0	0
submucosa; Congestion; few	2	0			0	1

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
INTESTINE, CECUM (Continued...)						
.... mild	2	0			0	1
submucosa; Edema; diffuse	2	0			1	2
.... mild	2	0			1	2
submucosa; Edema; focal	0	0			1	0
.... mild	0	0			1	0
submucosa; Edema; multifocal	1	2			2	1
.... mild	1	2			2	1
INTESTINE, COLON						
Examined	5	5			5	5
Normal	5	5			5	4
Not Examined: No Section	0	0			0	0
submucosa; Congestion; multifocal	0	0			0	1
.... mild	0	0			0	1
submucosa; Edema; multifocal	0	0			0	1
.... mild	0	0			0	1
INTESTINE, DUODENUM						
Examined	5	5			5	5
Normal	5	5			5	5
INTESTINE, ILEUM						
Examined	5	5			5	5
Normal	5	5			5	5
INTESTINE, JEJUNUM						
Examined	5	5			5	5
Normal	5	5			5	5
INTESTINE, RECTUM						
Examined	4	5			5	5
Normal	4	5			5	5
Not Examined: No Section	1	0			0	0
submucosa; Congestion; few	0	0			0	0
.... mild	0	0			0	0
KIDNEYS						
Examined	5	5			5	5
Normal	3	1			2	1
Cast; few	0	0			0	1
.... minimal	0	0			0	1

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
KIDNEYS (Continued...)						
Fibrosis; focal	0	0			1	0
.... minimal	0	0			0	0
.... mild	0	0			1	0
Inflammation; few	1	0			0	0
.... minimal	1	0			0	0
.... mild	0	0			0	0
Inflammation; focal	0	0			0	0
.... minimal	0	0			0	0
Inflammation; multifocal	0	0			1	0
.... minimal	0	0			1	0
Mineralization; few	0	0			1	0
.... minimal	0	0			1	0
Mineralization; focal	0	0			0	0
.... minimal	0	0			0	0
epithelium; tubule; Regeneration; few	1	1			0	2
.... minimal	1	1			0	2
epithelium; tubule; Regeneration; focal	0	3			1	2
.... minimal	0	3			1	2
epithelium; tubule; Regeneration; multifocal	1	0			0	0
.... minimal	1	0			0	0
tubule; epithelium; Regeneration; multifocal	0	0			0	0
.... mild	0	0			0	0
Cyst; few	0	0			1	0
.... minimal	0	0			0	0
.... mild	0	0			1	0
Cyst; focal	0	0			0	0
.... minimal	0	0			0	0
Dilation	1	0			0	0
.... mild	1	0			0	0
LIVER						
Examined	5	5			5	5
Hematopoiesis; few	1	2			3	4
.... minimal	0	2			2	3
.... mild	1	0			1	1

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
LIVER (Continued...)						
Hematopoiesis; multifocal	1	0			0	0
.... mild	1	0			0	0
periportal; Inflammation; few	1	2			3	3
.... minimal	1	2			1	3
.... mild	0	0			2	0
periportal; Inflammation; multifocal	2	3			0	2
.... minimal	2	3			0	2
hepatocyte; Mitosis Increased; widespread	3	5			1	0
.... minimal	3	2			1	0
.... mild	0	2			0	0
.... moderate	0	1			0	0
.... marked	0	0			0	0
hepatocyte; cytoplasm; Vacuolation; diffuse	2	5			5	5
.... minimal	0	1			0	0
.... mild	1	4			4	5
.... moderate	1	0			1	0
hepatocyte; cytoplasm; Vacuolation; multifocal	3	0			0	0
.... minimal	1	0			0	0
.... mild	1	0			0	0
.... moderate	1	0			0	0
hepatocyte; cytoplasm; Fatty Infiltration; diffuse	0	0			0	0
.... minimal	0	0			0	0
hepatocyte; cytoplasm; Fatty Infiltration; multifocal	0	0			2	0
.... minimal	0	0			1	0
.... mild	0	0			1	0
hepatocyte; cytoplasm; Inclusion; eosinophilic, multifocal	1	0			0	0
.... mild	1	0			0	0
LUNGS WITH BRONCHI						
Examined	5	5			5	5
alveolus; Hemorrhage; acute, multifocal	5	5			5	5
.... minimal	2	5			1	4
.... mild	3	0			4	1
.... moderate	0	0			0	0

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1		Group 2			
	0 ug/kg IV	88.1 ug/kg IV			0 ug/kg IV	88.1 ug/kg IV
Number of Animals:	5	5			5	5
LUNGS WITH BRONCHI (Continued...)						
peribronchiolar; Hemorrhage; acute, few	0	0			0	0
.... minimal	0	0			0	0
peribronchiolar; Hemorrhage; acute, multifocal	0	0			0	0
.... mild	0	0			0	0
perivascular; Hemorrhage; acute, few	1	4			2	3
.... minimal	0	3			2	3
.... mild	1	1			0	0
perivascular; Hemorrhage; acute, multifocal	0	1			1	0
.... mild	0	1			1	0
.... moderate	0	0			0	0
alveolus; macrophage; Proliferation; diffuse	0	0			0	0
.... mild	0	0			0	0
alveolus; macrophage; Proliferation; few	0	0			1	0
.... minimal	0	0			1	0
alveolus; macrophage; Proliferation; multifocal	1	2			1	1
.... mild	1	2			1	1
macrophage; alveolus; Proliferation; multifocal	4	3			3	4
.... minimal	4	3			3	4
alveolus; Edema; multifocal	0	0			0	0
.... mild	0	0			0	0
perivascular; Edema; few	1	1			1	4
.... minimal	1	1			1	4
perivascular; Edema; multifocal	1	0			1	0
.... minimal	0	0			0	0
.... mild	1	0			1	0
artery; Mineralization; focal	1	2			1	1
.... minimal	1	2			1	1
peribronchiolar; Inflammation; focal	0	0			0	0
.... minimal	0	0			0	0
perivascular; Inflammation; few	0	0			0	2
.... minimal	0	0			0	2
perivascular; Inflammation; multifocal	0	0			2	0
.... mild	0	0			2	0

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
LYMPH NODE, MESENTERIC						
Examined	5	5			5	5
Normal	4	3			3	4
Hemorrhage; acute, few	1	1			2	1
.... minimal	1	1			2	1
Hemorrhage; acute, multifocal	0	1			0	0
.... minimal	0	1			0	0
LYMPH NODE, MANDIBULAR						
Examined	5	5			5	5
Hemorrhage; acute, few	1	1			2	3
.... minimal	1	1			2	3
Hemorrhage; acute, multifocal	4	3			2	1
.... minimal	0	1			1	0
.... mild	4	1			1	1
.... moderate	0	1			0	0
Plasmacytosis	5	5			5	5
.... mild	3	3			1	4
.... moderate	2	2			2	0
.... marked	0	0			2	1
Hyperplasia; lymphoid	0	0			0	0
.... moderate	0	0			0	0
MAMMARY GLANDS						
Examined	3	5			5	5
Normal	3	5			5	5
Not Examined: Not Present	2	0			0	0
perivascular; Hemorrhage; acute, few	0	0			0	0
.... mild	0	0			0	0
SKELETAL MUSCLE						
Examined	5	5			5	5
Normal	5	5			5	5
NERVE, SCIATIC						
Examined	5	5			5	5
Normal	5	5			5	5
OVARIES						
Examined	.	.			5	5
Normal	.	.			5	5

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
OVARIES (Continued...)						
follicle; Cyst; few	.	.			0	0
.... mild	.	.			0	0
PANCREAS						
Examined	5	5			5	5
Normal	4	5			4	4
Inflammation; few	1	0			0	0
.... mild	1	0			0	0
periductal; Inflammation; few	0	0			0	1
.... minimal	0	0			0	1
periductal; Inflammation; focal	0	0			1	0
.... minimal	0	0			1	0
PARATHYROID GLAND						
Examined	5	4			5	4
Normal	5	4			5	4
Not Examined: Not Present	0	1			0	1
PITUITARY GLAND						
Examined	5	5			5	5
Normal	5	5			5	4
Cyst; few	0	0			0	0
.... minimal	0	0			0	0
Cyst; focal	0	0			0	1
.... minimal	0	0			0	1
PROSTATE GLAND						
Examined	5	5			.	.
Normal	5	5			.	.
Inflammation; multifocal	0	0			.	.
.... mild	0	0			.	.
SALIVARY GLAND, MANDIBULAR						
Examined	5	5			5	5
Normal	4	5			5	5
Hemorrhage; acute, few	1	0			0	0
.... minimal	1	0			0	0
acinar cell; cytoplasm; Inclusion; focal	0	0			0	0
.... moderate	0	0			0	0

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
SEMINAL VESICLES						
Examined	5	5			.	.
Normal	5	5			.	.
SKIN, VENTRAL ABDOMEN						
Examined	5	5			5	5
Normal	5	4			5	3
subcutaneous; Hemorrhage; acute, few	0	0			0	0
.... minimal	0	0			0	0
Acanthosis; focal	0	1			0	2
.... minimal	0	1			0	2
Hyperkeratosis; focal	0	1			0	0
.... minimal	0	1			0	0
Parakeratosis; few	0	0			0	1
.... minimal	0	0			0	1
dermis; Inflammation; few	0	0			0	1
.... minimal	0	0			0	1
SPINAL COLUMN						
Examined	5	5			5	5
Normal	5	5			5	5
SPINAL CORD, THORACOLUMBAR						
Examined	5	5			5	5
Normal	5	5			5	5
Hemorrhage; acute, few	0	0			0	0
.... minimal	0	0			0	0
Hemorrhage; acute, focal	0	0			0	0
.... minimal	0	0			0	0
SPLEEN						
Examined	5	5			5	5
Congestion	5	5			5	4
.... mild	4	4			4	2
.... moderate	1	1			1	2
Hematopoiesis	5	5			5	5
.... mild	5	4			3	4
.... moderate	0	1			2	1
.... marked	0	0			0	0

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:	5	5	5	5	
STOMACH, INCLUDING NONGLANDULAR						
Examined	5	5			5	5
Normal	1	0			0	1
mucosa; glandular; Hemorrhage; acute, few	0	1			0	0
.... minimal	0	1			0	0
non-glandular; epithelium; Hyperplasia; multifocal	0	0			0	0
.... mild	0	0			0	0
glandular; submucosa; Inflammation; diffuse	0	0			0	0
.... mild	0	0			0	0
submucosa; glandular; Inflammation; few	1	2			2	1
.... minimal	1	2			2	1
submucosa; glandular; Inflammation; multifocal	3	3			2	2
.... minimal	1	1			0	0
.... mild	2	2			2	2
submucosa; non-glandular; Inflammation; few	3	2			3	2
.... minimal	3	2			3	2
submucosa; non-glandular; Inflammation; multifocal	0	1			1	0
.... mild	0	1			1	0
non-glandular; epithelium; Hyperkeratosis; multifocal	0	0			0	0
.... mild	0	0			0	0
non-glandular; epithelium; Inclusion; few	0	0			0	0
.... minimal	0	0			0	0
TESTES						
Examined	5	5			.	.
Normal	5	5			.	.
seminiferous tubule; Hemorrhage; acute, few	0	0			.	.
.... minimal	0	0			.	.
THYMUS						
Examined	5	5			5	5
Normal	2	2			2	3
Hemorrhage; acute, few	1	2			1	1
.... minimal	1	2			0	1
.... mild	0	0			1	0

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	5
THYMUS (Continued...)						
Hemorrhage; acute, focal	0	0			0	0
.... minimal	0	0			0	0
Hemorrhage; acute, multifocal	2	1			2	1
.... minimal	2	0			2	1
.... mild	0	1			0	0
THYROID GLAND						
Examined	5	5			5	5
Normal	3	2			1	4
Cyst; ultimobranchial, few	1	2			4	0
.... minimal	1	1			2	0
.... mild	0	1			2	0
Cyst; ultimobranchial, focal	1	1			0	1
.... minimal	1	1			0	1
Inflammation; focal	0	1			0	0
.... minimal	0	1			0	0
TRACHEA						
Examined	5	5			5	5
mucosa; Hemorrhage; acute, few	0	2			0	1
.... minimal	0	0			0	0
.... mild	0	2			0	1
mucosa; Hemorrhage; acute, focal	1	1			0	0
.... mild	1	1			0	0
mucosa; Hemorrhage; acute, multifocal	0	0			0	0
.... mild	0	0			0	0
mucosa; Hemorrhage; few	0	0			0	0
.... minimal	0	0			0	0
mucosa; Inflammation; multifocal	5	5			5	5
.... minimal	3	2			0	2
.... mild	2	3			5	3
.... moderate	0	0			0	0
mucosa; glands; Dilation; multifocal	5	5			5	5
.... minimal	1	0			1	0
.... mild	1	2			2	0
.... moderate	1	2			1	3

General Footnote: [. Not Applicable]

Histopathology Summary

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Removal Reason: Recovery Sacrifice	Male				Female	
	Group 1 0 ug/kg IV		Group 2 88.1 ug/kg IV		Group 1 0 ug/kg IV	
	Number of Animals:		5	5	5	
TRACHEA (Continued...)						
.... marked	2	1			1	2
URINARY BLADDER						
Examined	5	5			4	5
Normal	5	5			4	4
Not Examined: No Section	0	0			1	0
submucosa; Edema; diffuse	0	0			0	1
.... moderate	0	0			0	1
submucosa; Congestion; multifocal	0	0			0	1
.... mild	0	0			0	1
UTERUS						
Examined	.	.			5	5
Normal	.	.			3	4
Dilation	.	.			2	1
.... mild	.	.			0	1
.... moderate	.	.			1	0
.... marked	.	.			1	0
VAGINA						
Examined	.	.			5	5
Normal	.	.			5	5

General Footnote: [. Not Applicable]

**Single Dose Toxicity Study of ER176 in Sprague Dawley Rats
SRI Study No. M038-13**

Appendix I-3

INDIVIDUAL ANIMAL HISTOPATHOLOGY DATA

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	001	Group:	1 - Vehicle	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
HEART : Hemorrhage; acute, few, minimal
INTESTINE, CECUM : submucosa; Congestion; few, mild
INTESTINE, CECUM : submucosa; Edema; diffuse, mild
KIDNEYS : epithelium; tubule; Regeneration; focal, minimal
LIVER : Hematopoiesis; few, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, marked
LIVER : hepatocyte; cytoplasm; Vacuolation; multifocal, moderate
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
SPINAL CORD, THORACOLUMBAR : Hemorrhage; acute, focal, minimal
SPLEEN : Congestion; moderate
SPLEEN : Hematopoiesis; moderate
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilatation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; TESTES; THYMUS; THYROID GLAND; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	002	Group:	1 - Vehicle	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BONE, STERNUM (MARROW HISTOLOGY) : Myelofibrosis; focal, mild
BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
HEART : Hemorrhage; acute, few, minimal
INTESTINE, CECUM : submucosa; Edema; diffuse, mild
KIDNEYS : epithelium; tubule; Regeneration; multifocal, minimal
LIVER : Hematopoiesis; few, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, moderate
LIVER : hepatocyte; cytoplasm; Vacuolation; multifocal, moderate
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Edema; multifocal, mild
LUNGS WITH BRONCHI : artery; Mineralization; focal, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; moderate
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, few, minimal
THYROID GLAND : Cyst; ultimobranchial, focal, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, mild

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR; STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; EPIDIDYMIDES; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	003	Group:	1 - Vehicle	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
HEART : Hemorrhage; acute, few, minimal
KIDNEYS : epithelium; tubule; Regeneration; few, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, moderate
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : alveolus; macrophage; Proliferation; multifocal, mild
LUNGS WITH BRONCHI : peribronchiolar; Inflammation; focal, minimal
LUNGS WITH BRONCHI : perivascular; Inflammation; few, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
LYMPH NODE, MANDIBULAR : Hyperplasia; lymphoid, moderate
PROSTATE GLAND : Inflammation; multifocal, mild
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
THYMUS : Hemorrhage; acute, multifocal, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, mild

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; THYROID GLAND; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

MAMMARY GLANDS - Not Present

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	004	Group:	1 - Vehicle	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
HEART : Hemorrhage; acute, few, minimal
KIDNEYS : epithelium; tubule; Regeneration; multifocal, minimal
LIVER : periportal; Inflammation; multifocal, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, moderate
LIVER : hepatocyte; cytoplasm; Vacuolation; multifocal, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, mild
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LYMPH NODE, MESENTERIC : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, few, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; THYROID GLAND; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

MAMMARY GLANDS - Not Present

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	005	Group:	1 - Vehicle	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

ADRENAL GLANDS : cortex; Hypertrophy; nodular, few, minimal
BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, mild
BRAIN (FORE-, MID-, HINDBRAIN) : ventricle; Dilation; mild
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : retina; Dysplasia; focal, minimal
HEART : Hemorrhage; acute, few, minimal
INTESTINE, CECUM : submucosa; Edema; multifocal, mild
KIDNEYS : Fibrosis; focal, minimal
KIDNEYS : Inflammation; few, minimal
KIDNEYS : epithelium; tubule; Regeneration; few, minimal
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, mild
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, moderate
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Edema; few, minimal
LYMPH NODE, MESENTERIC : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, minimal
TESTES : seminiferous tubule; Hemorrhage; acute, few, minimal
THYMUS : Hemorrhage; acute, multifocal, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; SKELETAL MUSCLE; NERVE, SCATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYROID GLAND; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

MAMMARY GLANDS - Not Present

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	006	Group:	1 - Vehicle	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, mild
KIDNEYS : Inflammation; few, minimal
KIDNEYS : epithelium; tubule; Regeneration; few, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, moderate
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : artery; Mineralization; focal, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
PANCREAS : Inflammation; few, mild
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, multifocal, minimal
THYROID GLAND : Cyst; ultimobranchial, focal, minimal
TRACHEA : mucosa; Inflammation; multifocal, minimal
TRACHEA : mucosa; glands; Dilation; multifocal, marked

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); HEART; INJECTION SITE; INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	007	Group:	1 - Vehicle	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

ADRENAL GLANDS : cortex; Hypertrophy; nodular, few, mild
BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, mild
HEART : Hemorrhage; acute, few, minimal
KIDNEYS : epithelium; tubule; Regeneration; multifocal, minimal
KIDNEYS : Dilation; mild
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; multifocal, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, mild
LUNGS WITH BRONCHI : alveolus; macrophage; Proliferation; multifocal, mild
LYMPH NODE, MESENTERIC : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
SPLEEN : Congestion; moderate
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; THYMUS; THYROID GLAND; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	008	Group:	1 - Vehicle	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, mild
HEART : Hemorrhage; acute, few, minimal
INTESTINE, CECUM : submucosa; Congestion; few, mild
INTESTINE, CECUM : submucosa; Edema; diffuse, mild
LIVER : periportal; Inflammation; multifocal, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; multifocal, minimal
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
SALIVARY GLAND, MANDIBULAR : Hemorrhage; acute, few, minimal
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, multifocal, minimal
TRACHEA : mucosa; Hemorrhage; acute, focal, mild
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, marked

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; KIDNEYS; LYMPH NODE, MESENTERIC; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; THYROID GLAND; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

INTESTINE, RECTUM - No Section
MAMMARY GLANDS - Not Present

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	009	Group:	1 - Vehicle	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : retina; Dysplasia; few, minimal
HEART : Hemorrhage; acute, few, minimal
HEART : Inflammation; focal, minimal
INTESTINE, CECUM : submucosa; Congestion; few, mild
INTESTINE, CECUM : submucosa; Edema; multifocal, mild
LIVER : Hematopoiesis; multifocal, mild
LIVER : periportal; Inflammation; multifocal, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; multifocal, moderate
LIVER : hepatocyte; cytoplasm; Inclusion; eosinophilic, multifocal, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Edema; few, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
TRACHEA : mucosa; Inflammation; multifocal, minimal
TRACHEA : mucosa; glands; Dilation; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR; STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; KIDNEYS; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND; MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD; THORACOLUMBAR; TESTES; THYMUS; THYROID GLAND; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	010	Group:	1 - Vehicle	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : retina; Dysplasia; multifocal, mild
HEART : Hemorrhage; acute, few, minimal
INTESTINE, CECUM : submucosa; Edema; diffuse, mild
LIVER : Hematopoiesis; few, mild
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Edema; multifocal, mild
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
THYMUS : Hemorrhage; acute, few, minimal
THYROID GLAND : Cyst; ultimobranchial, few, minimal
TRACHEA : mucosa; Inflammation; multifocal, minimal
TRACHEA : mucosa; glands; Dilatation; multifocal, mild

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; KIDNEYS; LYMPH NODE, MESENTERIC; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; STOMACH, INCLUDING NONGLANDULAR; TESTES; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

MAMMARY GLANDS - Not Present

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	011	Group:	1 - Vehicle	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, mild
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : periocular; Hemorrhage; acute, focal, mild
HEART : Hemorrhage; acute, few, minimal
INTESTINE, CECUM : submucosa; Edema; multifocal, mild
KIDNEYS : epithelium; tubule; Regeneration; multifocal, minimal
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : artery; Mineralization; focal, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SPLEEN : Congestion; moderate
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
THYROID GLAND : Cyst; ultimobranchial, few, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilatation; multifocal, mild

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYMUS; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

PARATHYROID GLAND - Not Present

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	012	Group:	1 - Vehicle	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, mild
BRAIN (FORE-, MID-, HINDBRAIN) : ventricle; Dilation; mild
KIDNEYS : Fibrosis; focal, minimal
KIDNEYS : Inflammation; few, mild
KIDNEYS : tubule; epithelium; Regeneration; multifocal, mild
LIVER : periportal; Inflammation; few, mild
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : alveolus; macrophage; Proliferation; multifocal, mild
LUNGS WITH BRONCHI : perivascular; Edema; multifocal, mild
LUNGS WITH BRONCHI : perivascular; Inflammation; multifocal, mild
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
SPLEEN : Congestion; moderate
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
THYMUS : Hemorrhage; acute, few, minimal
TRACHEA : mucosa; Hemorrhage; few, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); HEART; INJECTION SITE; INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYROID GLAND; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	013	Group:	1 - Vehicle	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : periocular; Hemorrhage; acute, focal, mild
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : Inflammation; multifocal, minimal
HEART : Hemorrhage; acute, few, minimal
KIDNEYS : tubule; epithelium; Regeneration; multifocal, mild
LIVER : Hematopoiesis; few, mild
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, moderate
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : alveolus; macrophage; Proliferation; multifocal, mild
LUNGS WITH BRONCHI : perivascular; Edema; few, minimal
LUNGS WITH BRONCHI : perivascular; Inflammation; multifocal, mild
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
OVARIES : follicle; Cyst; few, mild
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : glandular; submucosa; Inflammation; diffuse, mild
THYMUS : Hemorrhage; acute, few, minimal
THYROID GLAND : Cyst; ultimobranchial, few, mild
TRACHEA : mucosa; Inflammation; multifocal, mild

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR; STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; INJECTION SITE; INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	014	Group:	1 - Vehicle	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : retina; Dysplasia; few, minimal
HEART : Hemorrhage; acute, few, minimal
INTESTINE, CECUM : submucosa; Edema; diffuse, mild
KIDNEYS : Inflammation; few, minimal
KIDNEYS : epithelium; tubule; Regeneration; multifocal, minimal
KIDNEYS : Cyst; focal, minimal
LIVER : periportal; Inflammation; few, mild
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, moderate
LIVER : hepatocyte; cytoplasm; Fatty Infiltration; multifocal, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Inflammation; few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SPINAL CORD, THORACOLUMBAR : Hemorrhage; acute, few, minimal
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : glandular; submucosa; Inflammation; diffuse, mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, few, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; THYROID GLAND; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	015	Group:	1 - Vehicle	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : retina; Dysplasia; few, minimal
HEART : Hemorrhage; acute, few, minimal
INTESTINE, CECUM : submucosa; Edema; diffuse, mild
LIVER : hepatocyte; Mitosis Increased; widespread, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, moderate
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
PITUITARY GLAND : Cyst; few, minimal
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, few, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilatation; multifocal, mild
UTERUS : Dilatation; marked

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); BRAIN (FORE-, MID-, HINDBRAIN); CERVIX; ESOPHAGUS; INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; KIDNEYS; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYROID GLAND; URINARY BLADDER; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	016	Group:	1 - Vehicle	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

ADRENAL GLANDS : cortex; Hypertrophy; nodular, few, mild
BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
BRAIN (FORE-, MID-, HINDBRAIN) : ventricle; Dilation; mild
INTESTINE, CECUM : submucosa; Edema; multifocal, mild
KIDNEYS : epithelium; tubule; Regeneration; focal, minimal
LIVER : Hematopoiesis; few, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
PANCREAS : periductal; Inflammation; focal, minimal
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, few, mild
THYROID GLAND : Cyst; ultimobranchial, few, mild
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, mild
UTERUS : Dilation; moderate

Histo Pathology - The following Tissues were Within Normal Limits:

AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); HEART; INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; URINARY BLADDER; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	017	Group:	1 - Vehicle	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

ADRENAL GLANDS : cortex; Hypertrophy; nodular, few, minimal
BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
HEART : Inflammation; multifocal, mild
INTESTINE, CECUM : submucosa; Edema; diffuse, mild
KIDNEYS : Fibrosis; focal, mild
KIDNEYS : Inflammation; multifocal, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LIVER : hepatocyte; cytoplasm; Fatty Infiltration; multifocal, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : alveolus; macrophage; Proliferation; multifocal, mild
LUNGS WITH BRONCHI : perivascular; Edema; multifocal, mild
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; marked
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; moderate
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, multifocal, minimal
THYROID GLAND : Cyst; ultimobranchial, few, mild
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, marked
UTERUS : Dilation; marked

Histo Pathology - The following Tissues were Within Normal Limits:

AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD; THORACOLUMBAR; VAGINA

Histo Pathology - The following Tissues were Not Examined:

URINARY BLADDER - No Section

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	018	Group:	1 - Vehicle	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

ADRENAL GLANDS : cortex; Hypertrophy; nodular, few, mild
BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
BRAIN (FORE-, MID-, HINDBRAIN) : ventricle; Dilation; mild
ESOPHAGUS : submucosa; Inflammation; focal, minimal
HEART : Hemorrhage; acute, few, minimal
INTESTINE, CECUM : submucosa; Edema; focal, mild
LIVER : Hematopoiesis; few, minimal
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : alveolus; macrophage; Proliferation; few, minimal
LUNGS WITH BRONCHI : artery; Mineralization; focal, minimal
LUNGS WITH BRONCHI : perivascular; Inflammation; multifocal, mild
LYMPH NODE, MESENTERIC : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; multifocal, mild
THYMUS : Hemorrhage; acute, multifocal, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; KIDNEYS; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYROID GLAND; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	019	Group:	1 - Vehicle	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
BRAIN (FORE-, MID-, HINDBRAIN) : ventricle; Dilation; mild
LIVER : Hematopoiesis; few, mild
LIVER : periportal; Inflammation; few, mild
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LIVER : hepatocyte; cytoplasm; Fatty Infiltration; multifocal, minimal
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Edema; few, minimal
LUNGS WITH BRONCHI : perivascular; Inflammation; multifocal, mild
LYMPH NODE, MESENTERIC : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SPLEEN : Congestion; moderate
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYROID GLAND : Cyst; ultimobranchial, few, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, mild

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); HEART; INJECTION SITE; INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; KIDNEYS; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYMUS; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	020	Group:	1 - Vehicle	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 1 0ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, mild
HEART : Hemorrhage; acute, few, mild
INTESTINE, CECUM : submucosa; Edema; multifocal, mild
KIDNEYS : Mineralization; few, minimal
KIDNEYS : Cyst; few, mild
LIVER : periportal; Inflammation; few, mild
LIVER : hepatocyte; Mitosis Increased; widespread, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, moderate
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; marked
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; moderate
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYROID GLAND : Cyst; ultimobranchial, few, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, minimal

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SIT; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYMUS; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	021	Group:	2 - ER176	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
HEART : Hemorrhage; acute, few, minimal
INTESTINE, CECUM : submucosa; Edema; multifocal, mild
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, mild
LIVER : hepatocyte; cytoplasm; Vacuolation; multifocal, moderate
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : peribronchiolar; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Edema; few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; moderate
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, multifocal, mild
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilatation; multifocal, mild

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; KIDNEYS; LYMPH NODE, MESENTERIC; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; THYROID GLAND; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

MAMMARY GLANDS - Not Present

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	022	Group:	2 - ER176	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
 BRAIN (FORE-, MID-, HINDBRAIN) : ventricle; Dilation; mild
 EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : periocular; Hemorrhage; acute, focal, mild
 EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : periocular; Inflammation; few, minimal
 HEART : Hemorrhage; acute, few, minimal
 INTESTINE, CECUM : submucosa; Congestion; few, mild
 INTESTINE, CECUM : submucosa; Edema; diffuse, mild
 KIDNEYS : epithelium; tubule; Regeneration; multifocal, minimal
 LIVER : periportal; Inflammation; few, mild
 LIVER : hepatocyte; Mitosis Increased; widespread, moderate
 LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
 LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, mild
 LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
 LUNGS WITH BRONCHI : perivascular; Edema; few, minimal
 LUNGS WITH BRONCHI : perivascular; Inflammation; few, minimal
 LYMPH NODE, MESENTERIC : Hemorrhage; acute, few, minimal
 LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, moderate
 LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
 LYMPH NODE, MANDIBULAR : Hyperplasia; lymphoid, moderate
 PANCREAS : periductal; Inflammation; focal, minimal
 PROSTATE GLAND : Inflammation; multifocal, mild
 SPLEEN : Congestion; mild
 SPLEEN : Hematopoiesis; moderate
 STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
 THYROID GLAND : Cyst; ultimobranchial, focal, minimal
 TRACHEA : mucosa; Hemorrhage; acute, multifocal, mild
 TRACHEA : mucosa; Inflammation; multifocal, moderate
 TRACHEA : mucosa; glands; Dilation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; SKELETAL MUSCLE; NERVE, SCIATIC; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; THYMUS; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

MAMMARY GLANDS - Not Present

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	023	Group:	2 - ER176	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
 BRAIN (FORE-, MID-, HINDBRAIN) : ventricle; Dilation; mild
 EPIDIDYMIDES : duct; lumen; Debris; few, minimal
 EPIDIDYMIDES : duct; lumen; Hypocellularity; spermatozoal, marked
 HEART : Hemorrhage; acute, few, minimal
 INTESTINE, CECUM : submucosa; Congestion; few, mild
 INTESTINE, CECUM : submucosa; Edema; multifocal, mild
 INTESTINE, RECTUM : submucosa; Congestion; few, mild
 KIDNEYS : Inflammation; few, minimal
 KIDNEYS : epithelium; tubule; Regeneration; multifocal, minimal
 LIVER : hepatocyte; Mitosis Increased; widespread, marked
 LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
 LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
 LUNGS WITH BRONCHI : peribronchiolar; Hemorrhage; acute, multifocal, mild
 LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, multifocal, mild
 LUNGS WITH BRONCHI : alveolus; macrophage; Proliferation; multifocal, mild
 LUNGS WITH BRONCHI : perivascular; Edema; multifocal, mild
 LYMPH NODE, MESENTERIC : Hemorrhage; acute, multifocal, minimal
 LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
 LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
 SALIVARY GLAND, MANDIBULAR : acinar cell; cytoplasm; Inclusion; focal, moderate
 SPINAL CORD, THORACOLUMBAR : Hemorrhage; acute, few, minimal
 SPLEEN : Congestion; mild
 SPLEEN : Hematopoiesis; marked
 STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
 STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
 THYMUS : Hemorrhage; acute, few, minimal
 TRACHEA : mucosa; Hemorrhage; acute, few, minimal
 TRACHEA : mucosa; Inflammation; multifocal, mild
 TRACHEA : mucosa; glands; Dilation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; TESTES; THYROID GLAND; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	024	Group:	2 - ER176	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
 BRAIN (FORE-, MID-, HINDBRAIN) : ventricle; Dilation; mild
 EPIDIDYMIDES : duct; lumen; Hypocellularity; spermatozoal, mild
 HEART : Hemorrhage; acute, few, minimal
 INJECTION SITE: TAIL, ENTIRE : perivascular; Hemorrhage; acute, focal, minimal
 INJECTION SITE: TAIL, ENTIRE : perivascular; Inflammation; focal, minimal
 INTESTINE, CECUM : mucosa; Congestion; multifocal, mild
 KIDNEYS : Mineralization; focal, minimal
 LIVER : periportal; Inflammation; few, minimal
 LIVER : hepatocyte; Mitosis Increased; widespread, moderate
 LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
 LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, moderate
 LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, multifocal, moderate
 LUNGS WITH BRONCHI : alveolus; macrophage; Proliferation; diffuse, mild
 LUNGS WITH BRONCHI : alveolus; Edema; multifocal, mild
 LUNGS WITH BRONCHI : perivascular; Edema; multifocal, minimal
 LUNGS WITH BRONCHI : perivascular; Inflammation; multifocal, mild
 LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, minimal
 LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
 MAMMARY GLANDS : perivascular; Hemorrhage; acute, few, mild
 SPLEEN : Congestion; mild
 SPLEEN : Hematopoiesis; moderate
 STOMACH, INCLUDING NONGLANDULAR : non-glandular; epithelium; Hyperplasia; multifocal, mild
 STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
 STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
 STOMACH, INCLUDING NONGLANDULAR : non-glandular; epithelium; Hyperkeratosis; multifocal, mild
 STOMACH, INCLUDING NONGLANDULAR : non-glandular; epithelium; Inclusion; few, minimal
 THYMUS : Hemorrhage; acute, few, minimal
 TRACHEA : mucosa; Inflammation; multifocal, minimal
 TRACHEA : mucosa; glands; Dilation; multifocal, mild

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; THYROID GLAND; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	025	Group:	2 - ER176	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
EPIDIDYMIDES : Aspermia; present
EPIDIDYMIDES : duct; lumen; Debris; diffuse, mild
HEART : Hemorrhage; acute, few, minimal
INTESTINE, CECUM : submucosa; Edema; multifocal, mild
KIDNEYS : Inflammation; few, mild
KIDNEYS : epithelium; tubule; Regeneration; multifocal, minimal
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, mild
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : peribronchiolar; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Inflammation; few, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, moderate
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; moderate
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, few, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; THYROID GLAND; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

INTESTINE, COLON - No Section
MAMMARY GLANDS - Not Present

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	026	Group:	2 - ER176	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
HEART : Inflammation; few, minimal
KIDNEYS : epithelium; tubule; Regeneration; focal, minimal
LIVER : periportal; Inflammation; multifocal, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, mild
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, mild
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SKIN, VENTRAL ABDOMEN : Acanthosis; focal, minimal
SKIN, VENTRAL ABDOMEN : Hyperkeratosis; focal, minimal
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, few, minimal
THYROID GLAND : Cyst; ultimobranchial, focal, minimal
TRACHEA : mucosa; Hemorrhage; acute, few, mild
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, mild

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND; MANDIBULAR; SEMINAL VESICLES; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	027	Group:	2 - ER176	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
HEART : Epicarditis; focal, minimal
INTESTINE, CECUM : submucosa; Edema; multifocal, mild
KIDNEYS : epithelium; tubule; Regeneration; focal, minimal
LIVER : Hematopoiesis; few, minimal
LIVER : periportal; Inflammation; multifocal, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, moderate
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Edema; few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, multifocal, mild
THYROID GLAND : Cyst; ultimobranchial, few, minimal
THYROID GLAND : Inflammation; focal, minimal
TRACHEA : mucosa; Inflammation; multifocal, minimal
TRACHEA : mucosa; glands; Dilation; multifocal, mild

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR; STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

PARATHYROID GLAND - Not Present

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	028	Group:	2 - ER176	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, mild
BRAIN (FORE-, MID-, HINDBRAIN) : ventricle; Dilation; mild
HEART : Hemorrhage; acute, few, minimal
KIDNEYS : epithelium; tubule; Regeneration; focal, minimal
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, mild
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : alveolus; macrophage; Proliferation; multifocal, mild
LUNGS WITH BRONCHI : artery; Mineralization; focal, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, minimal
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYROID GLAND : Cyst; ultimobranchial, few, mild
TRACHEA : mucosa; Inflammation; multifocal, minimal
TRACHEA : mucosa; glands; Dilation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; THYMUS; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	029	Group:	2 - ER176	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : retina; Dysplasia; few, mild
INTESTINE, CECUM : mucosa; Congestion; multifocal, mild
INTESTINE, CECUM : submucosa; Edema; multifocal, mild
KIDNEYS : epithelium; tubule; Regeneration; few, minimal
LIVER : Hematopoiesis; few, minimal
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, minimal
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : artery; Mineralization; focal, minimal
LYMPH NODE, MESENTERIC : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
SPLEEN : Congestion; moderate
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
TRACHEA : mucosa; Hemorrhage; acute, focal, mild
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR; STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; HEART; INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; THYMUS; THYROID GLAND; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	030	Group:	2 - ER176	Sex:	Male
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
BRAIN (FORE-, MID-, HINDBRAIN) : ventricle; Dilation; mild
HEART : Hemorrhage; acute, few, minimal
LIVER : periportal; Inflammation; multifocal, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : alveolus; macrophage; Proliferation; multifocal, mild
LYMPH NODE, MESENTERIC : Hemorrhage; acute, multifocal, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, moderate
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; moderate
STOMACH, INCLUDING NONGLANDULAR : mucosa; glandular; Hemorrhage; acute, few, minimal
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; multifocal, mild
THYMUS : Hemorrhage; acute, few, minimal
TRACHEA : mucosa; Hemorrhage; acute, few, mild
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, marked

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); EPIDIDYMIDES; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; KIDNEYS; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; PROSTATE GLAND; SALIVARY GLAND, MANDIBULAR; SEMINAL VESICLES; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; TESTES; THYROID GLAND; URINARY BLADDER

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	031	Group:	2 - ER176	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
HEART : Inflammation; focal, minimal
INJECTION SITE: TAIL, ENTIRE : perivascular; Inflammation; focal, mild
INJECTION SITE: TAIL, ENTIRE : vein; Degeneration; focal, moderate
KIDNEYS : Fibrosis; focal, minimal
KIDNEYS : Inflammation; few, minimal
KIDNEYS : epithelium; tubule; Regeneration; focal, minimal
KIDNEYS : Cyst; focal, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, moderate
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Inflammation; few, minimal
LYMPH NODE, MESENTERIC : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; marked
SKIN, VENTRAL ABDOMEN : subcutaneous; Hemorrhage; acute, few, minimal
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, moderate
UTERUS : Dilation; mild

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYMUS; THYROID GLAND; VAGINA

Histo Pathology - The following Tissues were Not Examined:

URINARY BLADDER - No Section

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	032	Group:	2 - ER176	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
INJECTION SITE: TAIL, ENTIRE : perivascular; Inflammation; focal, minimal
INTESTINE, CECUM : submucosa; Congestion; few, mild
INTESTINE, CECUM : submucosa; Edema; diffuse, mild
KIDNEYS : Mineralization; few, minimal
KIDNEYS : epithelium; tubule; Regeneration; multifocal, minimal
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; multifocal, moderate
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilatation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); HEART; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYMUS; THYROID GLAND; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	033	Group:	2 - ER176	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

HEART : Inflammation; few, minimal
HEART : epicardium; Inflammation; focal, minimal
KIDNEYS : Mineralization; few, minimal
KIDNEYS : epithelium; tubule; Regeneration; few, minimal
KIDNEYS : Cyst; few, minimal
LIVER : Hematopoiesis; few, minimal
LIVER : periportal; Inflammation; multifocal, minimal
LIVER : hepatocyte; Mitosis Increased; widespread, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, mild
LUNGS WITH BRONCHI : alveolus; macrophage; Proliferation; multifocal, mild
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, focal, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilatation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); BRAIN (FORE-, MID-, HINDBRAIN); CERVIX; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYROID GLAND; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	034	Group:	2 - ER176	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, mild
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : periocular; Inflammation; few, minimal
HEART : Inflammation; focal, minimal
KIDNEYS : Inflammation; focal, minimal
KIDNEYS : Mineralization; focal, minimal
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Edema; few, minimal
LUNGS WITH BRONCHI : perivascular; Inflammation; few, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
SPLEEN : Congestion; moderate
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, few, minimal
THYROID GLAND : Cyst; ultimobranchial, few, minimal
TRACHEA : mucosa; Inflammation; multifocal, minimal
TRACHEA : mucosa; glands; Dilation; multifocal, mild

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR; STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; INJECTION SITE; INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	035	Group:	2 - ER176	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Main Sacrifice		
Necropsy Date:	6/14/2013	Study Day (Week) of Death:	3 (1)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : periocular; Inflammation; few, minimal
HEART : Hemorrhage; acute, few, minimal
INTESTINE, CECUM : submucosa; Congestion; few, mild
INTESTINE, CECUM : submucosa; Edema; multifocal, mild
KIDNEYS : epithelium; tubule; Regeneration; focal, minimal
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, minimal
LIVER : hepatocyte; cytoplasm; Fatty Infiltration; diffuse, minimal
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; moderate
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, multifocal, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYROID GLAND; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

INJECTION SIT - Not Examined: Lost At Necropsy

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	036	Group:	2 - ER176	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
BRAIN (FORE-, MID-, HINDBRAIN) : ventricle; Dilation; mild
INTESTINE, CECUM : submucosa; Edema; multifocal, mild
KIDNEYS : Cast; few, minimal
KIDNEYS : epithelium; tubule; Regeneration; focal, minimal
LIVER : Hematopoiesis; few, minimal
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : alveolus; macrophage; Proliferation; multifocal, mild
LUNGS WITH BRONCHI : perivascular; Edema; few, minimal
LUNGS WITH BRONCHI : artery; Mineralization; focal, minimal
LUNGS WITH BRONCHI : perivascular; Inflammation; few, minimal
LYMPH NODE, MESENTERIC : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SKIN, VENTRAL ABDOMEN : Acanthosis; focal, minimal
SKIN, VENTRAL ABDOMEN : Parakeratosis; few, minimal
SKIN, VENTRAL ABDOMEN : dermis; Inflammation; few, minimal
SPLEEN : Congestion; moderate
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, few, minimal
TRACHEA : mucosa; Inflammation; multifocal, minimal
TRACHEA : mucosa; glands; Dilation; multifocal, marked

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); HEART; INJECTION SIT; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYROID GLAND; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	037	Group:	2 - ER176	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL) : retina; Dysplasia; few, mild
INTESTINE, CECUM : submucosa; Congestion; few, mild
INTESTINE, CECUM : submucosa; Edema; diffuse, mild
KIDNEYS : epithelium; tubule; Regeneration; focal, minimal
LIVER : periportal; Inflammation; multifocal, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
PANCREAS : periductal; Inflammation; few, minimal
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; non-glandular; Inflammation; few, minimal
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilatation; multifocal, marked

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; HEART; INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYMUS; THYROID GLAND; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

None

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	038	Group:	2 - ER176	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
HEART : Hemorrhage; acute, few, minimal
HEART : Inflammation; few, minimal
KIDNEYS : epithelium; tubule; Regeneration; few, minimal
LIVER : Hematopoiesis; few, minimal
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Edema; few, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SKIN, VENTRAL ABDOMEN : Acanthosis; focal, minimal
SPLEEN : Congestion; mild
SPLEEN : Hematopoiesis; mild
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; few, minimal
THYMUS : Hemorrhage; acute, multifocal, minimal
THYROID GLAND : Cyst; ultimobranchial, focal, minimal
TRACHEA : mucosa; Inflammation; multifocal, minimal
TRACHEA : mucosa; glands; Dilation; multifocal, moderate
UTERUS : Dilation; mild

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE MARROW SMEAR; STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SIT; INTESTINE, CECUM; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; URINARY BLADDER; VAGINA

Histo Pathology - The following Tissues were Not Examined:

PARATHYROID GLAND - Not Present

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	039	Group:	2 - ER176	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

ADRENAL GLANDS : cortex; Hypertrophy; nodular, few, minimal
BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, mild
BRAIN (FORE-, MID-, HINDBRAIN) : ventricle; Dilatation; mild
INTESTINE, COLON : submucosa; Congestion; multifocal, mild
INTESTINE, COLON : submucosa; Edema; multifocal, mild
LIVER : Hematopoiesis; few, minimal
LIVER : periportal; Inflammation; few, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, mild
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Edema; few, minimal
LUNGS WITH BRONCHI : perivascular; Inflammation; few, minimal
LYMPH NODE, MANDIBULAR : Plasmacytosis; marked
PITUITARY GLAND : Cyst; focal, minimal
SPLEEN : Congestion; moderate
SPLEEN : Hematopoiesis; mild
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilatation; multifocal, moderate
URINARY BLADDER : submucosa; Edema; diffuse, moderate
URINARY BLADDER : submucosa; Congestion; multifocal, mild

Histo Pathology - The following Tissues were Within Normal Limits:

AORTA; BONE MARROW SMEAR, STERNUM CYTOLOGY; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); HEART; INTESTINE, CECUM; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; KIDNEYS; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; STOMACH, INCLUDING NONGLANDULAR; THYMUS; THYROID GLAND; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

INJECTION SIT - Not Examined: Not Collected

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Animal:	040	Group:	2 - ER176	Sex:	Female
Species:	Rat	Strain:	Sprague Dawley		
		Dose:	Group 2 88.1ug/kg IV		
		Removal Reason:	Recovery Sacrifice		
Necropsy Date:	6/26/2013	Study Day (Week) of Death:	15 (3)		

Histo Pathology Animal Details:

No animal details found

Histo Pathology Observations [Correlation]:

BRAIN (FORE-, MID-, HINDBRAIN) : Hemorrhage; acute, multifocal, minimal
HEART : Hemorrhage; acute, few, minimal
INTESTINE, CECUM : submucosa; Edema; diffuse, mild
KIDNEYS : epithelium; tubule; Regeneration; few, minimal
LIVER : Hematopoiesis; few, mild
LIVER : periportal; Inflammation; multifocal, minimal
LIVER : hepatocyte; cytoplasm; Vacuolation; diffuse, mild
LUNGS WITH BRONCHI : alveolus; Hemorrhage; acute, multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Hemorrhage; acute, few, minimal
LUNGS WITH BRONCHI : macrophage; alveolus; Proliferation; multifocal, minimal
LUNGS WITH BRONCHI : perivascular; Edema; few, minimal
LYMPH NODE, MANDIBULAR : Hemorrhage; acute, multifocal, mild
LYMPH NODE, MANDIBULAR : Plasmacytosis; mild
SPLEEN : Hematopoiesis; moderate
STOMACH, INCLUDING NONGLANDULAR : submucosa; glandular; Inflammation; multifocal, mild
TRACHEA : mucosa; Hemorrhage; acute, few, mild
TRACHEA : mucosa; Inflammation; multifocal, mild
TRACHEA : mucosa; glands; Dilatation; multifocal, moderate

Histo Pathology - The following Tissues were Within Normal Limits:

ADRENAL GLANDS; AORTA; BONE, FEMUR WITH FEMORO-TIBIAL JOINT; BONE, STERNUM; BONE, STERNUM (MARROW HISTOLOGY); CERVIX; ESOPHAGUS; EYES WITH OPTIC NERVE (FIXED WITH FORMOL ALCOHOL); INJECTION SITE; INTESTINE, COLON; INTESTINE, DUODENUM; INTESTINE, ILEUM; INTESTINE, JEJUNUM; INTESTINE, RECTUM; LYMPH NODE, MESENTERIC; MAMMARY GLANDS; SKELETAL MUSCLE; NERVE, SCIATIC; OVARIES; PANCREAS; PARATHYROID GLAND; PITUITARY GLAND; SALIVARY GLAND, MANDIBULAR; SKIN, VENTRAL ABDOMEN; SPINAL COLUMN; SPINAL CORD, THORACOLUMBAR; THYMUS; THYROID GLAND; URINARY BLADDER; UTERUS; VAGINA

Histo Pathology - The following Tissues were Not Examined:

BONE MARROW SMEAR, STERNUM CYTOLOGY - No Section

Histo Pathology - The following Protocol Required Tissues were Not Processed:

None

Histo Pathology - Additional Completeness Checks:

No additional completeness checks found

Individual Histopathology

M038-13 - Single Dose Toxicity Study of ER176 in Sprague Dawley Rats

Key Page

Codes

(TGL) = Trackable Gross Lesion, (MPF) = Major Pathological Finding, (?) = Questionable, (E) = Excluded,
(C) = Clinical Observation, (M) = Mass, (G) = Gross Pathology, (H) = Histo Pathology

Group Information

<u>Short Name</u>	<u>Long Name</u>
1	Vehicle
2	ER176