A DOSE RANGE-FINDING INTRAVENOUS INFUSION TOXICITY STUDY IN DOGS

MPI Research Proposal Number <> for <>

STUDY DESIGN: 18 dogs (9 / sex) + __ extra

<table>
<thead>
<tr>
<th>Phase A</th>
<th>MTD Study</th>
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</thead>
<tbody>
<tr>
<td>Dose Level 1</td>
<td>Males: 1 / Females: 1</td>
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<tr>
<td></td>
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<tr>
<td>Dose Level 2</td>
<td>Males: * / Females: *</td>
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<tr>
<td>Dose Level 3</td>
<td>Males: * / Females: *</td>
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<tr>
<td>Dose Level 4</td>
<td>Males: * / Females: *</td>
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<table>
<thead>
<tr>
<th>Phase B</th>
<th>MTD Study</th>
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<tbody>
<tr>
<td>Control</td>
<td>Males: 2 / Females: 2</td>
</tr>
<tr>
<td>Low Dose</td>
<td>Males: 2 / Females: 2</td>
</tr>
<tr>
<td>Mid Dose</td>
<td>Males: 2 / Females: 2</td>
</tr>
<tr>
<td>High Dose</td>
<td>Males: 2 / Females: 2</td>
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</tbody>
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7-Day Range Finding Study

PHYSICAL EXAMINATIONS: Conducted by staff veterinarian on all animals prior to initiation of dosing

PREPARATION OF THE ANIMALS: Approximately 1 week following arrival, the animals will undergo surgery for the implantation of a medical-grade catheter in a femoral vein. The animals will be allowed approximately 2 weeks between the surgical procedures and the initiation of dosing to recover. During this period, the animals will receive 0.9% Sodium Chloride for Injection, USP, in order to maintain patency of the infusion line.

EXPERIMENTAL DESIGN: In Phase A, the dose level will be adjusted (increased or decreased) until the maximum tolerated dose (MTD) is determined. The same animals will be re-used for each dose level following an appropriate washout period. The MTD is a dose that produces neither mortality nor more than a 10% decrement in body weight nor clinical signs of toxicity. In Phase B, animals will be dosed daily for 7 days at fractions of the single dose MTD to estimate a repeat dose MTD.

DOSE ROUTE/FREQUENCY:
Phase A: One male and one female will receive a single ___-minutes/hours intravenous infusion via a jacket and tether system followed by a ___-day washout period. Subsequent doses will be administered in the same manner at a dose level adjusted (increased or decreased) based on the absence or presence of signs of toxicity observed following the previous dose(s), until the MTD is determined.
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DOGS

Phase B: The test and control articles will be administered a daily -minutes/hours intravenous infusion via a jacket and tether system, for 7 consecutive days.

OBSERVATIONS: Twice daily (mortality/moribundity) on both Phases

DETAILED CLINICAL OBSERVATIONS: Twice daily in both Phases, starting on Day -1

INCISION SITES CHECK: Once daily following surgery (both Phases)

BODY WEIGHTS: Daily in both Phases, starting on Day -1

FOOD CONSUMPTION: Daily in both Phases, starting on Day -1

CLINICAL PATHOLOGY (Phase B Only): Hematology, coagulation, clinical chemistry, and urinalysis evaluations pretest and on all surviving animals prior to termination (i.e., on Day 8)

TOXICOKINETICS (Phase B Only): Blood collected on Days 1 and 7 at 6 timepoints/animal/day; TK analysis and modeling at additional costs.

NECROPSY (Phase B Only): All animals; tissues will be collected and preserved for possible future histopathological evaluation

ORGAN WEIGHTS (Phase B Only): Adrenals, brain, heart, kidneys, liver, lungs, ovaries with oviducts, pituitary, prostate, salivary glands, spleen, thyroid with parathyroid, thymus, testes, uterus

STATISTICAL ANALYSIS: Due to the small group size, group means and standard deviations only will be calculated

ANALYTICAL/BIOANALYTICAL: Dose formulation and TK samples will be shipped to the Sponsor for analysis

REGULATORY COMPLIANCES: GLP

STUDY PRICE: $
APPENDIX A: CLINICAL PATHOLOGY

Hematology Parameters Evaluated
- leukocyte count (total and differential)
- erythrocyte count
- hemoglobin
- hematocrit
- mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration (calculated)
- absolute and percent reticulocytes
- platelet count

Coagulation Parameters Evaluated
- prothrombin time
- activated partial thromboplastin time
- fibrinogen

Clinical Chemistry Parameters Evaluated
- alkaline phosphatase
- total bilirubin (with direct bilirubin if total bilirubin exceeds 1 mg/dL)
- aspartate aminotransferase
- alanine aminotransferase
- gamma glutamyl transferase
- sorbitol dehydrogenase
- urea nitrogen
- creatinine
- total protein
- albumin
- globulin and A/G (albumin/globulin) ratio (calculated)
- glucose
- total cholesterol
- electrolytes (sodium, potassium, chloride)
- calcium
- phosphorus

Urinalysis Parameters Evaluated
- volume
- specific gravity
- pH
- color and appearance
- protein
- glucose
- bilirubin
- ketones
- occult blood
- urobilinogen
- microscopy of spun deposit

To receive information about this study, please contact Ms. Elen LeBel at Elen.Lebel@mpiresearch.com or call 269-668-3336.