A DOSE RANGE-FINDING INTRAVENOUS INFUSION TOXICITY STUDY IN RATS

MPI Research Proposal Number < > for < >

STUDY DESIGN: 118 rats (59/sex) + extra

<table>
<thead>
<tr>
<th>Phase A</th>
<th>MTD Study</th>
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<tbody>
<tr>
<td></td>
<td>Males</td>
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<tr>
<td>Dose Level 1</td>
<td>3</td>
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<td>Dose Level 2</td>
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<td>Dose Level 3</td>
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<td>Dose Level 4</td>
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<tr>
<th>Phase B</th>
<th>7-Day Range Finding Study</th>
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<tr>
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<td>Main Study</td>
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<td>Toxikokinetics</td>
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<td>Males</td>
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<tr>
<td>Control</td>
<td>5</td>
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<tr>
<td>Low Dose</td>
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<tr>
<td>Mid Dose</td>
<td>5</td>
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<tr>
<td>High Dose</td>
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PREPARATION OF THE ANIMALS: The animals will be purchased with a previously implanted femoral catheter exteriorized between the scapulae. Prior to the initiation of dosing, 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 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: The first group of animal will receive a single __ minutes/hours intravenous infusion via a jacket and tether system followed by a __ day observation period. Subsequent groups will be dosed in the same manner at a dose level adjusted based on the absence or presence of signs of toxicity observed in the previous group(s), until the MTD is determined.
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 in both Phases (mortality/moribundity)

DETAILED CLINICAL OBSERVATION: Daily in both Phases, starting on Day -1

INCISION SITES CHECK: Daily, following arrival (both Phases)

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

FOOD CONSUMPTION: Daily, starting on Day -1

CLINICAL PATHOLOGY (Phase B only): Hematology, coagulation, and clinical chemistry evaluations on all surviving Main study animals at termination (i.e., Day 8). See Appendix A.
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TOXICOKINETICS (Phase B only): Blood collected on Days 1 and 7 (3 cohorts consisting of 3 animals/sex/treatment group bled twice to equal six timepoints; TK analysis and modeling at additional costs.

NECROPSY (Phase B only): All animals, tissues (approximately 65) 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, seminal vesicles, spleen, thyroid with parathyroid, thymus, testes, uterus

STATISTICAL ANALYSIS (Phase B only): Standard

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

REGULATORY COMPLIANCES: GLP

STUDY PRICE: $
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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

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 1-269-668-3336.