The objective of the study was to evaluate the toxicity (Tox) of a known stimulant when administered via IV infusion to Sprague Dawley rats immunized with an 86 dose of test article on study days 1, 22, and 64. Cardiovascular (CV) and Pharmacokinetic (PK) data were also collected following stimulant infusion on days 86 and 149.

The study initiated with 116 M and 116 F rats (Toxicology-60/sex; Pharmacokinetic-24/sex; Cardiovascular Telemetry-32/sex). The animals were checked for patency and treated with 0.5% hexylated saline every other week. Two animals were electively euthanized due to ulceration and inflammation of the skin around the exteriorized port. Other early deaths (11 across control and test article groups were not considered to be test article-related or related to the catheter or port. There were no test article-related effects on clinical observation. Test article-related, slightly decreased body weight gains were observed for all animals during each week following test article administration. Decreased body weight gains and decreased food consumption were also noted following the stimulant infusions. Differences in hematology, serum chemistry, coagulation and urinalysis were successfully attributed to test-article administration and not hindered by the presence of catheters or ports.

The pharmacokinetic evaluation of the implanted rats showed minimal variability between sexes and exhibited the anticipated dose-response curve of the stimulant interacting with the test article. Therefore, the implantation of the vascular access button did not result in responses from the animals that would hinder the interpretation of this study design.

Infusion dosing for 15 seconds, once every ten minutes for one hour on study days 86 and 149 was successful. The set-up of the pumps allowed dosing to occur while staff was outside the study room for the Cardiovascular animals. Catheters remained patent for dosing for the entirety of the study. Bi-directional patency rates for the Toxicology animals (Table 1) and Pharmacokinetic and Cardiovascular animals (Table 2) were well above expectations at our facility.

The pharmacokinetic evaluation of the implanted rats showed minimal variability between sexes and exhibited the anticipated dose-response curve of the stimulant interacting with the test article. Therefore, the implantation of the vascular access button did not result in responses from the animals that would hinder the interpretation of this study design.

### RESULTS

#### 1 ABSTRACT

The Infusion Department at Charles River Ashland was given a challenge: administer a 15 second intravenous dose to rats every ten minutes for one hour on study days 86 and 149; A surgically implanted catheter was used to allow for intravenous infusion via an infusion pump. Due to the study design, several areas of concern were noted, including the extended duration of the study, weighing concerns for patency, the condition of the port, and social housing for animal welfare. An extended port using magnetic connections was determined to be the best option with consideration given to animal growth, catheter length, and tip style; security of the catheter to the port, while also allowing for social housing. The study initiated with 116 M and 116 F rats (Toxicology-60/sex; Pharmacokinetic-24/sex; Cardiovascular Telemetry-32/sex). The animals were checked for patency and treated with 0.5%, hexylated saline every other week. Two animals were electively euthanized due to compromised port. Of the surviving animals, 98% of the Toxicology animals remained bi-directionally patent until scheduled main and recovery necropsy on study days 87 and 130 respectively and 96% of the Pharmacokinetic and Cardiovascular remained bi-directionally patent until scheduled necropsy on study day 131. System refinements (catheter tip style and security) facilitated the exceptional patency rates, the successful dosing of the study, and allowed for social housing for most of the study.

#### 2 METHODS

The use of an externalized magnetic port allowed for study required periodic infusions which would have been very difficult using a subcutaneous vascular access port and would not have been possible with the use of an internalized catheter. The metal projection cap allowed social housing during the non-infusion dosing periods.

A bi-directional catheter was maintained via every other week flush/lock regimen and adherence to aseptic technique. Also, there were no clinical or gross necropsy findings or changes in white blood cell counts to indicate the presence of infection.

The simplicity of the non-programable pumps allowed the pumps to be placed on the same circuit and the 70 second IV infusion doses were successfully administered every 15 minutes on study days 86 and 149. It also allowed for undisturbed collection of cardiovascular data.

#### 3 RESULTS

Infusion dosing for 15 seconds, once every ten minutes for one hour on study days 86 and 149 was successful. The set-up of the pumps allowed dosing to occur while staff was outside the study room for the Cardiovascular animals. Catheters remained patent for dosing for the entirety of the study. Bi-directional patency rates for the Toxicology animals (Table 1) and Pharmacokinetic and Cardiovascular animals (Table 2) were well above expectations at our facility.

Two animals were electively euthanized (study day 42 and 136) due to ulceration and inflammation of the skin around the externalized port. Other early deaths (11 across control and test article groups were not considered to be test article-related or related to the catheter or port. There were no test article-related effects on clinical observation. Test article-related, slightly decreased body weight gains were observed for all animals during each week following test article administration. Decreased body weight gains and decreased food consumption were also noted following the stimulant infusions. Differences in hematology, serum chemistry, coagulation and urinalysis were successfully attributed to test-article administration and not hindered by the presence of catheters or ports.

The pharmacokinetic evaluation of the implanted rats showed minimal variability between sexes and exhibited the anticipated dose-response curve of the stimulant interacting with the test article. Therefore, the implantation of the vascular access button did not result in responses from the animals that would hinder the interpretation of this study design.

### CONCLUSIONS

- The use of an externalized magnetic port allowed for study required periodic infusions which would have been very difficult using a subcutaneous vascular access port and would not have been possible with the use of an internalized catheter. The metal projection cap allowed social housing during the non-infusion dosing periods.
- A bi-directional catheter was maintained via every other week flush/lock regimen and adherence to aseptic technique. Also, there were no clinical or gross necropsy findings or changes in white blood cell counts to indicate the presence of infection.
- The simplicity of the non-programable pumps allowed the pumps to be placed on the same circuit and the 70 second IV infusion doses were successfully administered every 15 minutes on study days 86 and 149. It also allowed for undisturbed collection of cardiovascular data.

### Table 1

<table>
<thead>
<tr>
<th>ANIMALS</th>
<th>PATENCY RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicology</td>
<td>99%</td>
</tr>
<tr>
<td>Pharmacokinetic and Cardiovascular</td>
<td>99%</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>ANIMALS</th>
<th>PATENCY RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicology</td>
<td>99%</td>
</tr>
<tr>
<td>Pharmacokinetic and Cardiovascular</td>
<td>99%</td>
</tr>
</tbody>
</table>