An up to 6 Month Subcutaneous Infusion Qualification Study in Beagle Dogs

Emilie Langlois-Forget, Chloe Desjardins, Robert Tavcar, Mohamed Said Maghezzi, Julius Haruna, Roy Forster, Simon Authier

**TOXICOLOGY SERVICES**
- General toxicology in all species
- Special toxicology
- Infusion
- Inhalation
- Dermal
- Ocular
- Immunotoxicology
- Regenerative medicine
- Reproductive toxicology including minipigs and NHPs
- Carcinogenicity studies also in rasH2 and p53+/- mice
- Genetic toxicology: ICH compliant package
- In vitro toxicity: BCOP, h-CLAT, Keratin5+Sens™, DPRA, Photo 3T3-NR1F, EpiSkin™, chicken eye test
- Agrochemical / chemical / REACH
- QSAR
- Physico-chemical testing
- Ecotoxicology: wide range of test species

**SAFETY PHARMACOLOGY**
- Integrated safety pharmacology in toxicity studies
  - CV (JET), BP
  - Respiratory (JET), plethysmography
  - CNS (JET), BP
- In vitro assays
  - GLP compliant ion channel testing panel (HERG +5)
- CNE or vivo models for seizure liability screening
- Screening and follow-up models
  - Rodent and non-rodent LVF telemetry
  - Anaesthetized models
  - Polysomnography
  - Gastrointestinal motility

**DMPK, BIOANALYSIS, BIOMARKERS**
- ICH and ‘H ADME studies in all species
- In vitro metabolic clearance, metabolite ID and profiling, DD5 package (metabolism and transporters)
- Bioanalysis
  - LC/MS/MS, GC/MS/MS, LC-Radiodetection, ELISA, RIA
- Toxicogenomics, miRNA: Affymetrix™ accredited service provider, next generation sequencing (Illumina®)
- Immunology: 10-color flow cytometer, Luminex, Maso Scale

**MEDICAL DEVICE**
- Biocompatibility testing
- Cardiovascular stents, electrophysiology and structural heart studies
- Long-bone defects and cranio-maxillofacial/dental models
- Spinal fusion models
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**SPECIALIZED EXPERTISE**
- Juvenile studies including minipigs
- Otoxicity in rats
- Fertility studies in rodents and NHPs
- Radiation safety and efficacy studies
- Tissue Cross Reactivity (TCR): human and animal tissue banks
- Gene therapy vector biodistribution via ICPR
- ES cell testing: devTOX™ and cardioTOX™ (with Stemina)
- Lead optimization and predictive toxicology services: Leadscreen™

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**Citoxlab Group companies**

**Citoxlab France**
+33 (0)2 32 29 26 26
citoxlabfrance@citoxlab.com
B.P. 563 - 27005 Evreux Cedex,
France

**Citoxlab North America**
+1 888 563 2260
citoxlabnorthamerica@citoxlab.com
445, Armand-Frappier Blvd.
Laval, Quebec, H7V 4B3,
Canada

**Citoxlab Denmark**
+45 56 86 15 00
citoxlabdenmark@citoxlab.com
Hestehavevej 36A, Ejby,
DK-4623 Lille Skensved,
Denmark

**Citoxlab Hungary**
+36 48 545 300
citoxlabhun@citoxlab.com
Vízspárm, Szabadalagpuszta, 8200,
Hungary

**AccelLAB**
+1 415 435 9482
info@accellab.com - www.accellab.com
1635 Lionel-Bertrand Blvd.
Boisbriand, Quebec, J7H 1N8,
Canada

**Citoxlab USA / Xenometrics**
+1 913 850 5000
info@xenometricslc.com
www.xenometricslc.com
17745 Metcalf Ave, Stilwell, KS 66085,
USA

**Atlanbio**
+33 (0)2 51 10 01 00
atlanbio@atlanbio.com
www.atlanbio.com
1 Rue Graham Bell
Z.I du Bris
CS 40309
44605 Saint-Nazaire Cedex,
France

**Also Represented By**

Media Services Ltd
+81 3 3666 9915
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INTRODUCTION

Subcutaneous infusion is an important alternative route of administration that offers several advantages over other parenteral and non-parenteral routes. There are many devices already marketed for human use; however, translation into animal models can involve species specific challenges requiring technical and medical support. The surgical implantation of an internal medical grade subcutaneous catheter, accessed by an external catheter via a subcutaneous port, offers the ability to administer a larger volume with reduced chances of leakage compared to traditional implanted catheter and reduced maintenance and medical support compared to a standard catheter/port system.

MATERIALS AND METHODS

Five Beagle dogs/sex (9-10 months) were prepared with an internal subcutaneous port and catheter system. The external catheter was inserted into the internal catheter by accessing the subcutaneous port 6-8 days post-surgery. The external catheter was inserted into a tether/swivel system and connected to a syringe using a medical-grade tubing extension set. A catheter was inserted into a tether/swivel system and connected to a syringe using a medical-grade tubing extension set. The animals received physiological saline at a rate of 0.1 mL/hour for 2 weeks (3/sex) or 4-6 months (2/sex). All animals were catheterized by accessing the subcutaneous port 6-8 days post-surgery. The external catheter was inserted into a tether/swivel system and connected to a syringe using a medical-grade tubing extension set. The animals received physiological saline at a rate of 0.1 mL/hour for 2 weeks (3/sex) or 4-6 months (2/sex). All animals were catheterized by accessing the subcutaneous port 6-8 days post-surgery.

RESULTS

Appetite and Body Weights:

- Decreases in appetite and body weight losses were observed in most animals following surgery and connection to the infusion system for both study arms (Figure 2, A and B). For the 4-6-month arm the body weights increased through the study for 3 out 4 animals (A). The magnitude of these losses was minimized by the provision of wet food post-surgery for the animals included in the short-term arm (B).

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DISCUSSION AND CONCLUSION

- The results obtained in this study indicated that using a dual catheter with port system was superior to the traditional catheter implantation or standard port access system methods. There was virtually no possibility of leakage around the catheter exteriorsation site (allowing a greater infusion volume) as well as increased system stability. These results provided sufficient evidence that the subcutaneous infusion system was well tolerated in the test species and did not result in any unexpected histological changes other than those normally observed with surgically implanted catheters. Results from this study were subsequently confirmed in a 3-month GLP toxicity study in dogs.

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- Safety pharmacology core battery
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Citoxlab Group companies

Citoxlab France
+33 (0)2 32 29 26 26
contact.france@citoxlab.com
B.P. 563 - 27005 Evreux Cedex, France

Citoxlab North America
+1 888 553 2560
contact.northamerica@citoxlab.com
445, Armand-Frappier Blvd.
Laval, Quebec, H7V 4B3, Canada

Citoxlab Denmark
+45 56 86 15 00
contact.scanlab@citoxlab.com
Hestehavevej 36A, Elby,
DH-4621 Lille Skensved, Denmark

Citoxlab Hungary
+36 48 545-300
contact.hungary@citoxlab.com
Veszprém, Szabadságpuszta, 8200, Hungary

AccelLAB
+1 450 435 9482
info@accellab.com - www.accellab.com
1635 Lionel-Barrand Blvd.
Boisbriand, Quebec, J7H 1N8, Canada

Citoxlab USA / Xenometrics
+1 913 850 5000
info@xenometricsllc.com
www.xenometricsllc.com
17745 McCall Ave, Stilwell, KS 66085, USA

Atlanbio
+33 (0)2 51 10 01 00
atlanbio@atlanbio.com
www.atlanbio.com
1 Rue Graham Bell
Z.I de Brissac
CS 40309
44605 Saint-Nazaire Cedex, France

Also represented by

Media Services Ltd
+81.3 3666 9915
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