TOXICOLOGY SERVICES
- General toxicology: Rodents, Non-rodents: dogs, NHPs and minipigs
- Inhalation
- Dermal
- Ocular
- Immunotoxicology
- Reproductive toxicology including minipigs and NHPs
- Carcinogenicity studies also in rats and p53+/- mice
- Genetic toxicology: ICH compliant package
- In vitro toxicology: BCOOP, MUSH, DPEA, Photo 3T3, Episom™
- Agrochemical / Chemical / REACH
- QSAR
- Physical chemistry
- Ecotoxicology: wide range of test species

SAFETY PHARMACOLOGY
- Integrated Safety Pharmacology in Toxicology Studies
  - CV (JET), BP
  - Respiratory (JET), plethysmography
  - CNS (FOB) and JET-EEG
- Safety pharmacology core battery
- Early safety pharmacology screening
  - Rodent and non-rodent LVP telemetry
  - Anaesthetized models: ECG, ABP, LVP and QA

DMPK AND BIOMARKERS
- Radiolabeled DMPK: in all species
- Bioanalysis LC-MS/MS, GC-MS/MS, LC-ICP/MS, ELISA, RIA
- Toxicogenomics, miRNA: Affymetrix™ Accredited service provider, Next Generation Sequencing (Illumina™)
- Immunology: Flow cytometry, Luminescence, Mesoscale

SPECIALIZED EXPERTISE
- Juvenile studies including minipigs
- Fertility studies in rodents and NHPs
- Radiation safety and efficacy studies
- Tissue Cross Reactivity: human and animal tissue banks
- Gene therapy vector biodistribution via qPCR
- ES cell testing: devTOX™ and cardioTOX™ (with Stemina)
- Lead optimization and predictive toxicology services: Leadscreen™

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Functional Neurotoxicity Evaluation of Noribogaine using Video-EEG in Cynomolgus monkeys
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INTRODUCTION
Continuous Video-EEG monitoring remains the gold standard for seizure liability assessments. Noribogaine is the primary metabolite of ibogaine, an alkaloid derived from the African shrub, iboga (Tabernanthe iboga). Ibogaine has been explored as a treatment for substance dependence, but its psychotomimetic effects limit its clinical utility. Noribogaine may be more selective in treating opioid dependence without undesirable psychotomimetic effects. A study in healthy volunteers revealed safety and tolerability of single oral doses of 3-60 mg noribogaine, and that a slow half-life (28-49 hours) was noted with large volume of distribution (Glue et al., 2015). In a recent single ascending dose study in opioid-dependent participants, noribogaine (60-180mg) was well tolerated and demonstrated a concentration-dependent increase in QT interval (Glue et al., 2016). A multiple-dose safety study conducted by DemeRx is ongoing.

METHODS
Six cynomolgus monkeys (3 per gender) were instrumented with telemetry transmitters (C70-EEE, Data Science International) for continuous EEG recording using the 10-20 system (C3-O1, C4-O2 and Cz-Oz) as previously described (Authier et al., 2019). Animals were also instrumented with catheters for remote blood collection to allow TK sampling without handling stress. Video was recorded during EEG monitoring using day and infrared night vision cameras. Video-EEE was recorded for at least 24 hours prior to each dose to at least 24 hours after each dose. Video was used to support interpretation of EEG traces. The test and any reference item were administered by oral gavage in a dose escalation design with blood samples obtained using a remote collection system. Based on the plasma half-life of Noribogaine HCl measured in a previous monkey study, a wash-out period of at least 6 days was allowed between each treatment to eliminate the test item.

The positive control pentylene tetrozol (PTZ) was administered by intravenous infusion to freely moving animals using a catheter.

EEG traces were analyzed using the NeuroScore software (Data Science International).

RESULTS
Noribogaine HCl
Clinical signs such as excessive scratching and licking, chewing motion, emesis, partial anorexia, slightly decreased activity level, uncoordination and/or myoclonic jerks (myoclonic jerks were seen in only one monkey at this dose level) were noted at 160 mg/kg. Similar clinical signs were observed at the high dose level (320 mg/kg) but with higher incidence or severity. These behaviors were not associated with any EEG abnormality. EEG after Noribogaine HCl did not identify any seizure activity at any dose level. A single brief episode (~3 sec) of paroxysmal activity was observed in one monkey given 320 mg/kg but this was correlated with EMG artifacts.

Toxicokinetics on Day 21 (Treatment Session 4, 320 mg/kg) showed that maximum plasma concentrations of Noribogaine HCl were achieved between 2.5 and 24 h post-dosing in males and between 1 to 9 h in females with mean plasma concentrations (Cmax) of 614.93 and 299.93 ng/mL in males and females, respectively. The systemic exposure to Noribogaine HCl was similar in both genders as shown by the male to females Cmax and AUC(last) ratios of 1.13 and 1.15, respectively.

Positive control: Pentylene tetrozol (PTZ)
Clinical signs after PTZ intravenous infusion included retching, excessive scratching, repeated yawning, excessive vocalization, salivation, emesis, uncoordination, slight to severe decreased activity level (lying on cage floor myoclonic jerks, tremors and/or tonic convulsions. The infusion was immediately stopped upon presence of convulsions. Convulsions induced by PTZ were self-limited or were successfully controlled with a single dose of dizapam. EEG after continuous PTZ infusion was associated with episodes of synchronous neuronal depolarization with increasing amplitudes noted with crescendo until generalized convulsions in all animals. PTZ was invariably associated with EEG paroxismal activity at an average dose of 48 mg/kg and EEG seizure activity at an average dose of 54 mg/kg.

Thereafter, plasma concentration declined slowly, with mean plasma concentrations (Cmax) at 24th post-dose that were 614.93 and 299.93 ng/mL in males and females, respectively. The systemic exposure to Noribogaine HCl was similar in both genders as shown by the male to females Cmax and AUC(last) ratios of 1.13 and 1.15, respectively.

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CONCLUSION
EEG patterns were within normal limits following administration of Noribogaine at doses up to 320 mg/kg with concurrent central nervous system clinical signs that correlated with plasma exposures and resolved by the end of the monitoring period. Video-EEG monitoring using telemetry in cynomolgus monkeys allowed the assessment of Noribogaine safety and supported initiation of clinical trials.

REFERENCES