# Evaluation of The Safety of Surgical Implantation and Splenic Neurovascular Bundle Stimulation Using A Novel Implantable Cuff Via Histologic Assessment of The Splenic Artery and Abdominal and Thoracic Organs In A Porcine Model

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## Background:

- Electric stimulation of the Neurovascular Bundle, that encases the Splenic Artery (SpA-NVB), is being studied as an investigational immuno-modulation therapy for refractory Rheumatoid Arthritis.
- This novel system stimulates the SpA-NVB using a lead with electrodes within a cuff that is laparoscopically placed around the SpA-NVB.
- We present data from a preclinical validation study conducted to Good Laboratory Practice (GLP) standards that assessed the effects of:
  - Laparoscopic implantation of the lead
  - The presence of the cuff around the SpA-NVB
  - Stimulation of the SpA-NVB on the splenic artery, and thoracic and abdominal viscera.

## Laparoscopic Implant Procedure

- Yucatan pigs (N=26) were obtained from a commercial vendor, and were acclimated for 2 weeks prior to surgery
- All pigs received peri-operative analgesics and underwent induction of general anesthesia.
- Contrast angiography was performed to confirm normal splenic artery anatomy.
- Standard laparoscopic techniques and instrumentation were used to:
  - Isolate the SpA-NVB
  - Implant the cuff, encircling the SpA-NVB
- The lead body was then routed through the abdominal wall to a subcutaneous pocket where the Implantable Pulse Generator was placed.
- Postimplant angiography was performed to document the cuff location on the splenic artery NVB.

## Site and System Credentials:

- All study procedures and animal use were approved by the local Institutional Animal Care and Use Committee.
- All procedures and cares were performed in accordance with facility SOPs in an Association for Assessment and Accreditation of Laboratory Animal Care International accredited facility with approved Animal Welfare Assurance on file with the NIH Office for Laboratory Animal Welfare.
- This investigational system, is not commercially available, and is being studied in an Early Feasibility Study under an FDA IDE

## Postoperative Follow-up.

- After recovering from surgery, animals were randomly allocated to 30- or 90-days of further study, and for each time point to sham therapy or splenic nerve stimulation therapy
- Sham therapy or stimulation therapy was then initiated and the animals followed for 30- or 90-days of additional study.
- After completing the stimulation or sham therapy animals underwent angiography, were euthanized and underwent a full necropsy by a board-certified veterinary pathologist.

## Results:

- **Perioperative Management**
  - All animals were successfully managed according to the SOPs of the facility.
  - All animals underwent successful laparoscopic implantation of the lead
  - No procedure specific interventions were required.
  - All animals recovered fully from surgery
  - After recovery from surgery, animals were randomized to one of four groups:

| | Sham therapy | Stimulation therapy |
|---|---|---|
| 30-days of therapy | N = 6 | N = 6 |
| 90-days of therapy | N = 7 | N = 7 |

- **All animals survived to the study end points of 30-days or 90-days of sham or splenic stimulation therapy,**
- **Therapy was tolerated in all study groups.**

## Results:

- **Evaluation at the end of sham or splenic stimulation therapy:**
  - At the end of the study, all animals underwent angiography, were euthanized, and underwent necropsy and histological examination by a board-certified veterinary pathologist.
  - Evaluation of the **postimplant angiogram** revealed that the cuff remained in place around the SpA-NVB in all cases.
  - **Results of the histologic evaluation:**
    - There was no evidence of stenosis, erosion, thrombosis or inflammation in the splenic artery or vein.
    - The cuff and electrodes were encapsulated in a thin layer of connective tissue.
    - All general histological features in the cuff/artery interface were similar at 30 and 90-days of follow-up.
    - Minimal inflammatory changes were seen in the 30-day group and were less pronounced in animals in the 90-day group.
- **Summary of Findings**
  - These findings demonstrated the expected postoperative healing following surgical implantation of an implantable medical device.
  - The histologic findings for the therapy group were equivalent to the sham group at all timepoints, with no specimen demonstrating findings that would be associated with altered nerve function.
  - There was no evidence of procedure or therapy induced pathology in the abdominal or thoracic organs.

## Conclusions

- These data support the hypothesis that the implant procedure, the presence of the novel electrode containing cuff on the SpA-NVB, and the delivery of splenic stimulation therapy are not associated with pathologic alteration of the splenic artery, SpA-NVB, abdominal or thoracic viscera.
- These data support continued evaluation of this potential bioelectronic therapy in clinical trials.