From Feasibility Outcomes to Pivotal Study Design:
The First FDA IDE-Approved Implantable Neuromodulation Trial in Resistant Migraine

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Background

Current Gaps in Research

- Resistant migraine is defined by Delphi consensus as migraine with ≥8 monthly migraine days, severe disability, and failure of ≥3 preventive therapy classes
- People living with resistant migraine represent a high-burden population with substantial unmet needs
- Prior implantable neuromodulation trials have focused primarily on chronic migraine populations
- These studies were not designed using contemporary resistant migraine definitions[1]

[1] Robblee et al. Reaching international consensus on the definition of refractory migraine using the Delphi method. Cephalalgia. 2025 Sep;45(9):3331024251367767.

Investigational Approach

An investigational implantable neuromodulation system targeting the supraorbital and occipital nerves offers a potential treatment for resistant migraine, but requires prospective evaluation of several key factors:

- Feasibility
- Safety
- Patient compliance
- Device durability
- Blinding methodology

Three feasibility studies addressed these considerations and informed the design of the first FDA IDE-approved pivotal trial of an implantable neuromodulation device in people living with resistant migraine.

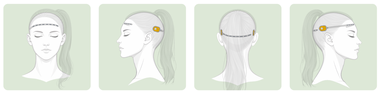
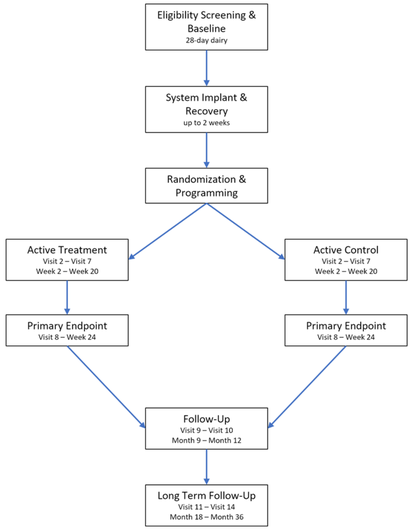


Figure 1 – System Overview. The implant is a battery-less implantable neurostimulator consisting of a stimulator and a thin, flexible lead with electrodes that deliver electrical stimulation to nerves. The 17 cm implant is placed at the back of the head to stimulate the left and right greater occipital nerves, while the 25 cm implant is placed at the front of the head to stimulate the left and right supra-orbital nerves (top panel). The implants are powered by an external wearable device through a wireless inductive link (bottom panel).

Study Flow Chart



Aspect	Details
Design	Prospective, multicenter, 1:1 randomized (Active R vs. Active Control P), double-blind, adaptive
Population	Adults with resistant migraine (Delphi criteria: ≥8 MMD, failure/intolerance/contraindication to ≥3 preventive classes incl. OnabotulinumtoxinA + CGRP mAbs, significant disability)
N	~150 randomized (up to 25 US sites)
Primary Endpoint	≥30% reduction in Monthly Migraine Days (MMD) at 24 weeks (weeks 20–24)
Key Secondary	Change in MMD, moderate-to-severe headache days (MHD), MSQ, MIDAS, PGIC

Table 1 – Key Design Characteristics.

Methods

Three feasibility studies, **RESPONSE**, **RELIEF**, and **RECLAIM** (ongoing - randomized, double-blind, sham-controlled), evaluated feasibility, safety, and durability in:

1. Chronic cluster headache
2. Chronic migraine
3. Resistant migraine

Findings from RECLAIM

- Insights from RECLAIM informed optimization of blinding strategies for the pivotal study design
- The study supports implementation of a perceptually matched active-control condition designed to maintain study blinding and integrity

Pivotal Trial Design

- Population: Adults with resistant migraine
- Randomization: 1:1 (active treatment vs. active control)
- Stimulation parameters will be optimized and personalized at 24 weeks
- Blinding:
  - Participants, investigators, & assessors blinded through Month 12
  - Programmers remain unblinded

Primary Endpoint

- ≥30% reduction in monthly migraine days (Weeks 20–24)

Adaptive Design Features

- Futility assessment
- Sample-size re-estimation
- Type I error control

Study	Indication	No. Patients Implanted[1]	No. Patients who underwent replacement[2]	No. Implant procedures (original + replacement)	Total treatment months	Implant duration months-median (min, max)
SCI-01-CCH: RESPONSE	Cluster Headache	3	2	5	75.6	24.5 (21.5, 29.6)
SCI-02-CM: RELIEF	Resistant Migraine	7	3	10	172.9	25.7 (14.9, 28.3)
SCI-03-RM: RECLAIM	Resistant Migraine	42	3	45	264.5	7.2 (0.7, 14.6)
TOTAL		**52**	**8**	**60**	**513.0**	

[1]Each patient was implanted with 2 devices (1 SONS and 1 ONS implant)
[2]In RESPONSE and RELIEF, both devices were replaced. In RECLAIM, only the affected device was replaced

Table 2 – Overview of Patient-Months Implanted in Clinical Investigations.

Results

Study Overview

- 3 feasibility studies
- 52 patients with SONS and ONS implants
- 100% procedural success

Safety Outcomes

- No device-related SAEs
- 3 procedure-related SAEs
  - All resolved
  - No long-term sequelae

Compliance & Durability

Exposure: *513 patient-months*

- High adherence
  - eDiary completion ≥82% (all patients)
  - Majority: 90–100% compliance
- Sustained device performance
  - Median implant duration: 7.2–25.7 months

Efficacy — RELIEF Study

- Mean reduction 5-day reduction in monthly migraine days (MMD)
- 71% responder rate
  - ≥30% reduction in MMD at 12 weeks

Clinical Implication

- Findings support safety, usability, and durability
- Data informed sample size assumptions for the pivotal trial

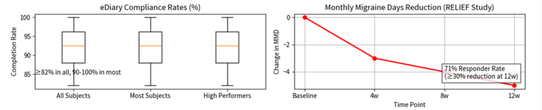


Figure 2 – eDiary Compliance Rates (left panel). Monthly Migraine Days Reduction (right panel).

Conclusion

Feasibility and Trial Design Overview

Feasibility data from 513 patient-months of exposure demonstrated procedural success and favorable safety, durability, and adherence findings that informed progression to the pivotal trial and current study design.

- Procedural success achieved in all implanted participants
- Safety: Device- and stimulation-related safety findings were favorable
- Durability: Sustained device performance over time
- Compliance: High patient adherence observed

Clinical Significance

This FDA IDE-approved pivotal trial targets resistant migraine, a population with substantial unmet need that has historically been excluded from implantable neuromodulation trials.

- Addresses high disease burden
- Expands access to novel treatment options
- Represents a critical step in evaluating a new therapeutic approach

Blinding and Study Integrity

- Participants, investigators, and site personnel involved in clinical assessments and data collection remain blinded through the 12-month follow-up period to minimize bias and reduce focus on treatment allocation.
- Participants in both treatment arms receive active stimulation. Standardized procedures, scripting, visit schedules, and identical implant/activation processes are used across groups to preserve blinding and study integrity.
- Programming adjustments are performed only by unblinded sponsor personnel, while participants and study staff are instructed to avoid discussions regarding perceived therapy or treatment assignment.

Disclosure
Salvia BioElectronics B.V. has supported this research and is the sponsor of RESPONSE, RELIEF, and RECLAIM early feasibility studies.