Enterra® Therapy System

Humanitarian Device Exemption (HDE) H990014

Pediatric Advisory Committee
September 12, 2017

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Device Description

Enterra is a surgically-implanted gastric electrical stimulator (GES) consisting of the following:

1. A neuro-stimulator placed in a subcutaneous abdominal pocket, which delivers electrical pulses
2. Two intramuscular leads implanted into the stomach greater curvature at the limit of the corpus-antrum
3. An external programmer

Indications for Use

Enterra is indicated for the treatment of patients with chronic, intractable (drug-refractory) nausea and vomiting secondary to gastroparesis [GP] of diabetic or idiopathic etiology in patients aged 18 to 70 years.

Annual Distribution Numbers

The Annual Distribution Number (ADN) is currently defined as the number of devices reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the U.S.

- The ADN for Enterra is 4,000 (based on original device approval)

The number of units sold since the 2016 PAC were:

- 1,865 neuro-stimulators
- 2,462 leads

The number of units implanted in 2016 reporting period were 93 total:

- 56 -first device implants (37 in 18 - 21 years old and 19 in <18 years)
- 37 -as device replacement in pediatric patients

Medical Device Report (MDR) Review

Search Criteria (FDA/CDRH Database):

- Report Time Period: May 1, 2016 to April 30, 2017
- Product Code: LNQ (Intestinal Stimulator)
- Brand Name: Enterra

Search Results:

- 404 Total MDRs*
- 15 Pediatrics (12 to <22 years)
- 271 Adults (≥ 22 years)
- 118 cases were indeterminate age

Event Type Distribution by Patient Age

Event Type	Total MDR Count	Pediatric (<22)	Adult (≥22)	No Reported Age (Indeterminate)
Death	2	0	1	1
Injury*	255	13	159	83
Malfunction**	144	2	109	33
Total	**401**	**15**	269	117

Three (3) MDRs were excluded since the events were reported in two journal ar1cles in April 2016, which is outside of the defined date range for this analysis

(*) *"Injury"* (CFR 803.3) includes an event that is life---threatening or results in permanent impairment of a body func1on or permanent damage to a body structure or necessitates medical or surgical interven1on(s) to preclude permanent impairment of a body func1on or permanent damage to a body structure.

(**) *"Malfunc/on"* (CFR 803.3) means the failure of a device to meet its performance specifica1ons or otherwise perform as intended; it is reportable when it is likely to cause or contribute to a death or serious injury if the malfunc1on were to recur.

Time to Event Occurrence (TTEO)*

Time to Event Occurrence (TTEO)	Pediatric (<22 y)	Adult (≥22 y)	Indeterminate (No Reported Age)
≤30 days	6	46	2
31 days – 364 days	4	65	8
1 – 5 years **≤ 21-months: All Pediatric pts**	5	113	18
>5 years	0	20	7
Totals (N=294)	**15**	244	35

* Time to Event Occurrence (TTEO) was calculated as the 1me between the date of Implant and the date of the Event.

Adverse Events in Pediatric Patients Year-to-Year Comparison

Adverse Events 5/2015 – 4/2016	Occurrences in MDRs*
Electric Shock/Nerve Simulation, Inappropriate Electric Shock	6
Nausea/Vomiting	4
Pain/Discomfort/ Abdominal Pain	2
Infection/Erosion	2

Adverse Events 5/2016 – 4/2017	Occurrences in MDRs*
Nausea/Vomiting	9
Pain/Discomfort/ Abdominal Pain	6
Therapeutic Response Decreased/Paresis	5
Infection/Wound Infection	3

(*) Note: Only the most observed pa1ent problems and issues contained in the narra1ves of the pediatric MDRs are included. Because a single MDR can contain mul1ple clinical events, the total number of occurrences in MDRs does not equal the total number of pediatric MDRs.

MDR Review - Conclusions

- Patient and device problems in Pediatric patients were similar to those observed in adults and indeterminate age

- More MDRs related lead malfunctions or connections (e.g., device impedance issues due to lead connection and/or battery) were reported this year. Manufacturer evaluation of the units was limited due to no device return in 352 of the 401 MDRs

- The reported issues are known inherent risks for the device and do not represent any new safety concern

Lee S, et al.

"Some non-FDA approved uses for neuromodulation in treating autonomic nervous system disorders: A Discussion of the preliminary support."

Neuromodulation 2016, 19:791-803

Summary:

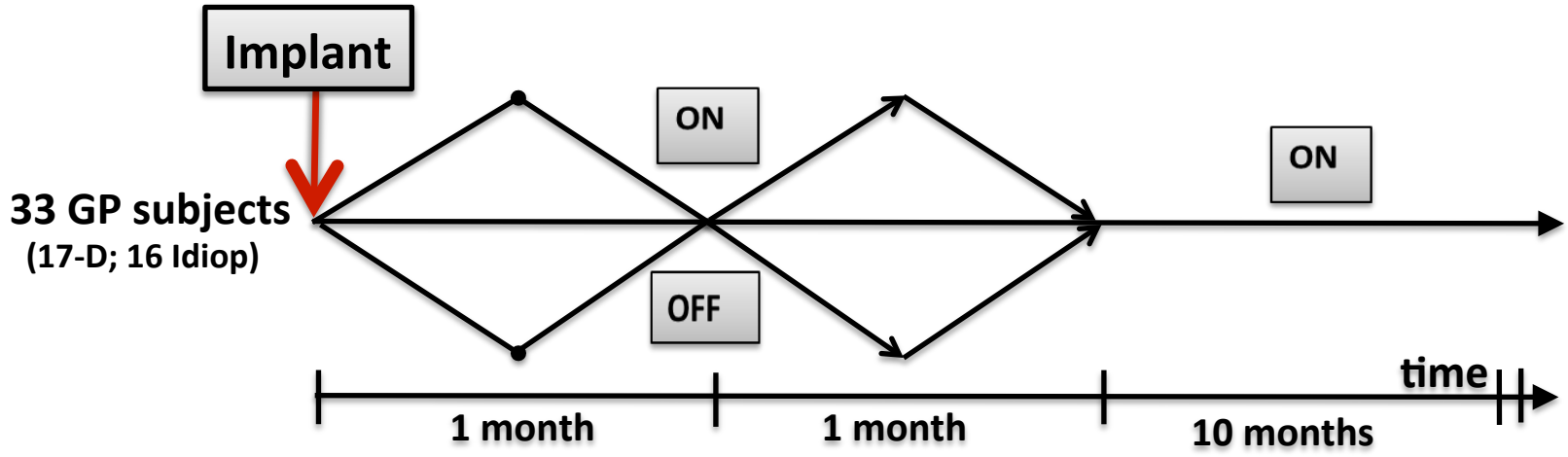
- Systematic literature review on neuromodulation treatment modalities and conditions for autonomic nervous system disorders: Gastric Electrical Stimulation (GES), Gastroparesis(GP), Vagus Nerve Stimulation, Asthma, and others

- The authors identified 4 papers involving results of GES for treatment of GP that met search criteria. Only 2 papers: **Abell et al., and McCallum et al. included Pediatric patients**

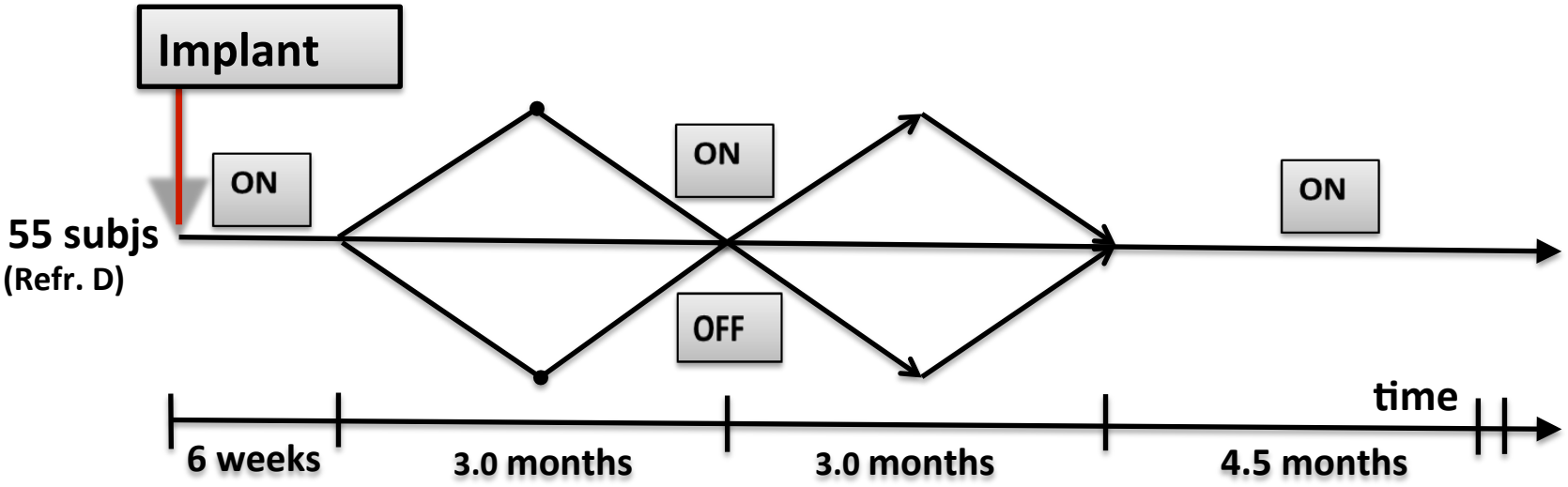
- **Abell et al., and McCallum et al.** did not meet the search criteria as they were published in 2003 and 2010, respectively, and included in the previous 2014 PAC meeting.

Study Design

Abell et al.



McCallum et al.



Abell et al. and McCallum et al. - Results

Probable Benefits

- Patients in “ON” mode treatment showed a greater reduction in median vomiting frequency than patients in “OFF” mode compared to baseline and study earlier time-points. The highest improvement was observed in the Diabetic cohort compared to Idiopathic and Refractory Diabetic patients
- Improvement in total symptoms and severity scores was also reported
- Gastric empting time was reported to be modestly accelerated or unchanged

Safety

- Most commonly reported Patient-related SAEs were: “Hospitalizations“ associated with GP symptoms (>32.8% of all patient-related AEs), ketoacidosis, vomiting, hematemesis, hypoglycemia, and hypertension
- Most commonly reported Device-related SAEs were: Device explant and device migration/dislodgment leading to surgical intervention due to site infection, erosion, or hematoma
- Total 7 deaths, -none of them was considered be device or therapy-related

Literature Review - Conclusions

- Improvement/reduction of upper GI symptoms. Effects on the need for nutritional support was not evaluated. Additional surgery may be required
- Device-related adverse events were consistent with those identified in previous literature reviews and in the product labeling (with exception of hematoma), and do not raise new safety concerns
- Literature review limitations:
  - Only one paper met search criteria
  - Study design issues (e.g., small sample size, short F/u, no data for the Pediatric cohort), and low level scientific evidence
  - Unclear if benefits reported in overall study population represented the Pediatric cohort of patients
- There is limited ability to make firm conclusions about the probable benefits and safety of Enterra in the Pediatric population

CDRH Recommendations

FDA will continue surveillance and report the following to the PAC in 2018:

- Annual Distribution Numbers
- MDR data
- Literature review results

Question to the PAC

Does the Committee agree with CDRH's conclusions and recommendations?

ACKNOWLEDGEMENT

Office of Device Evaluation

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Priya Venkataraman-Rao

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FDA
U.S. FOOD & DRUG
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