Boston Scientific

CLINICAL STUDY SUMMARY

ENABLE MRI

CAUTION: Federal Law restricts this device to sale by or on the order of a physician trained or experienced in device implant and follow-up procedures.

TABLE OF CONTENTS

CLINICAL STUDY – SUMMARY OF ENABLE MRI CLINICAL STUDY

The ENABLE MRI Clinical Study was designed to collect data to confirm the safety and effectiveness of the ImageReady™ MR Conditional Defibrillation System (hereafter referred to as the ImageReady System) when used in the 1.5T MRI environment under the labeled Conditions of Use.

The ImageReady System consists of specific Boston Scientific model components including pulse generators, leads, and accessories. The ImageReady MR Conditional Defibrillation System is labeled as "MR Conditional" as defined by the American Society for Testing and Materials (ASTM),[1] when used as a system and in accordance with the labeled MRI Conditions of Use.

STUDY DESIGN

The ENABLE MRI Study was a prospective, non-randomized, confirmatory study at multiple global centers.

For the study, *de novo* and existing implant subjects were enrolled and underwent a non-diagnostic study required MR Scan within 6 weeks, for existing implant subjects, or between 6-9 weeks after initial implant or surgical revision of the ImageReady System. Subjects had a study required follow up visit at one month post MRI (MRI + 1 Month Visit). Subjects will be followed annually for 3 years for adverse events and continued evaluation of the ImageReady System performance.

METHODS

Subject Selection

Subjects enrolled in the ENABLE MRI Study were selected from the investigators general patient population with an eligible existing ICD/CRT-D or indicated for an ICD or CRT-D implantation. The Investigator was responsible for screening potential subjects and selecting those who met the eligibility criteria for the study. Subjects who consented to be part of the VF Induction Sub-study also were evaluated for the VF Induction Sub-study exclusion criteria at the time of their consent.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Subject was indicated per guidelines and was to receive a CRT-D or ICD system consisting only of the following MR Conditional components* (OR) Subject is implanted with a functional and stable CRT-D or ICD system consisting only of Boston Scientific MR Conditional components. Subject was planned to receive or is implanted with an ICD or CRT-D pulse generator in the left or right pectoral region
- Subject was able and willing to undergo an MR scan without intravenous sedation
- Subject was willing and capable of providing informed consent and participating in all testing/ visits associated with this clinical study at an approved clinical study center and at the intervals defined by this protocol

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[1]ASTM Standard F2503-08, "Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment" ASTM International, West Conshohocken, PA, 2008, DOI: 10.1520/F2503-08, www. astm.org.

- Subject was age 18 or above, or of legal age to give informed consent specific to state and national law

Exclusion Criteria

- Subject implanted with an ICD or CRT-D pulse generator with battery at Explant status
- Subject had other active or abandoned implanted cardiac rhythm devices, components or accessories present such as pulse generators, leads, lead adaptors or extenders. Presence of metallic objects that represent a contraindication to MR imaging at the discretion of the Radiologist and impacting the ability to conduct the study protocol Known or suspected sensitivity to Dexamethasone acetate (DXA)
- Subject needs or will need a medically necessary MR scan, before completing the 1-month post-MR follow-up visit
- Subject with:
  - A history of syncope related to brady-arrhythmia
  - A history of syncope of unknown etiology
  - Sinus pauses (Pause > 2 s)
  - Permanent or intermittent complete AV block
  - Documentation of progressive AV nodal block over time
  - Trifascicular block (alternating bundle branch block or PR > 200 ms with LBBB or other bifascicular block)
- Subject was not clinically capable of tolerating the absence of pacing or Resynchronization therapy support in a supine position for the duration that the pulse generator is in MRI Protection Mode, per Physician discretion
- Subject was not clinically capable of tolerating the absence of Tachycardia therapy support for the duration that the pulse generator is in MRI Protection Mode, per Physician discretion
- Subjects with a planned RA, RV or LV lead revision or extraction within 30 days of enrollment
- Subjects with an implanted lead that was planned to be extracted during the study implant procedure
- Subjects requiring dialysis
- Subject with a mechanical heart valve
- Subject with a known or suspected sensitivity to dexamethasone acetate (DXA)
- Subject on the active heart transplant list
- Subject had documented life expectancy of less than 12 months
- Subject was enrolled in a concurrent study, with the exception of local mandatory governmental registries and observational studies/registries, without the written approval from Boston Scientific
- Women of childbearing potential who were or might be pregnant, and were to receive an ICD or CRT-D pulse generator

ENABLE MRI Study Endpoints

Safety Endpoint

- MR Scan-related ImageReady System Complication-Free Rate between the MR Scan and the MRI + 1 Month Visit

Effectiveness Endpoints

- Primary RV Effectiveness Endpoint 1: Increase in RV pacing threshold (at 0.5 ms) from the pre-MR scan to the 1 Month post-MR Scan
- Primary RV Effectiveness Endpoint 2: Decrease in RV Sensed Amplitude from the pre-MR scan to the 1 Month post-MR Scan
- Primary LV Effectiveness Endpoint 1: Increase in LV pacing threshold (at 0.5 ms) from the pre-MR scan to the 1 Month post-MR Scan
- Primary LV Effectiveness Endpoint 2: Decrease in LV Sensed Amplitude from the pre-MR scan to the 1 Month post-MR Scan

RESULTS

Safety and efficacy results through the MRI +1 Month Visit are included in this ENABLE MRI Clinical Study Summary. A total of 237 subjects were enrolled in the PMA cohort.

A summary of subject disposition is shown in Figure 1 on the following page.

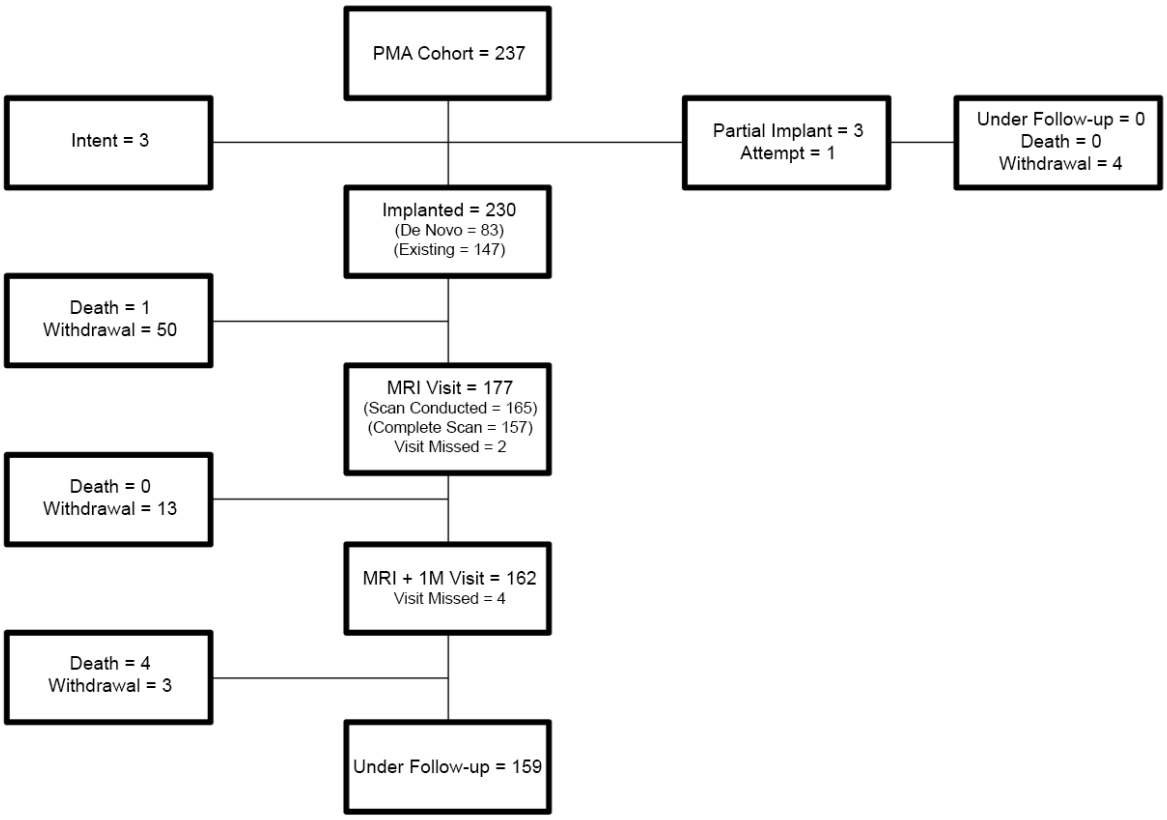

Figure 1: Subject Disposition

Subject Demographics

Table 1 summarizes the baseline demographics for the ENABLE MRI subjects. Overall, the average age of the subjects was 65 ± 12 years, with an overall gender ratio of 27.5% female to 72.6% male.

Table 1: Subject Demographics
(N = 237 All Enrolled Subjects)

Characteristic	Measurement	Result
Age at Implant (years)	Mean ± SD (Median) Range	65 ± 12 (66) 34-89
Sex [N (%)]	Female	65 (27.5)
	Male	172 (72.6)
BMI (kg/m^2)	Mean ± SD (Median) Range	28.5 ± 6.2 (27.8) 15.6-50.1

Table 2: Subject Implant Information summarizes the implant information for the ENABLE MRI subjects. Both existing implant subjects and *de novo* subjects were enrolled. Most subjects were implanted or had a pre-existing CRT-D device (N = 191, 83.0%) compared to ICD (N = 39, 17.0%).

Table 2: Subject Implant Information
(N = 230 All Implanted Subjects)

Characteristic	Measurement	Results
PG Type [N (%)]	CRT-D	191 (83.0)
	VR ICD	39 (17.0)
PG Model [N (%)]	INOGEN™ X4 CRT-D	94 (40.9)
	DYNAGEN™ X4 CRT-D	87 (37.8)
	INOGEN™ EL ICD	18 (7.8)
	DYNAGEN™ EL ICD	11 (4.8)
	AUTOGEN™ X4 CRT-D	10 (4.3)
	AUTOGEN™ EL ICD	6 (2.6)
	ORIGEN™ MINI ICD	2 (0.9)
	AUTOGEN™ MINI ICD	1 (0.4)
	INOGEN™ MINI ICD	1 (0.4)

Study Endpoint Results

Safety and effectiveness endpoints are summarized below. Adverse events reported by the investigators were reviewed and classified by an internal committee. All complications reported by the study investigator as related to the MRI scan and all subject deaths were further adjudicated by an independent Clinical Events Committee (CEC).

Safety Endpoint Results

A summary of the Primary Safety Endpoint result is shown in Table 3.

Table 3: Primary Safety Endpoint Result Summary

Endpoint	Assessment	One sided Alpha	Performance Result (Confidence Interval)	Performance Goal	Conclusion
Primary Safety	MR Scan-Related ImageReady System Complication-Free Rate	2.5%	100.00% (100.00%)	90%	Endpoint Met

Primary Safety Endpoint: MR Scan-Related ImageReady System Complication Free Rate

The Primary Safety Endpoint was assessed for all subjects that underwent any portion of the study-required MR scan sequences. However, if a medically necessary scan occurred between implant and the MRI + 1 Month Visit, data for that subject was not included in this endpoint.

Safety was confirmed by evaluating the MR scan-related ImageReady System Complication-free rate (CFR) between the MR Scan and the MRI Visit + 1 Month (calculated as MR scan + 31 days). For the purpose of this endpoint, a MR scan-related ImageReady System complication was defined as those complications that were related to the MR scan and ImageReady System.

The MR Scan related complication-free rate through 31 days post MRI Scan was 100% with a one-sided 97.5% lower confidence limit of 100%. The lower confidence limit is greater than the performance goal of 90.0%, resulting in a rejection of the null hypothesis.

Effectiveness Endpoints Results

The effectiveness endpoints were designed to detect a permanent increase in pacing threshold or decrease in sensed amplitude resulting from an MR scan. An MR scan may induce damage to cardiac tissue surrounding the lead distal electrode which is fixated in the myocardium. The potential tissue damage resulting from RF field-induced heating was clinically assessed by evaluating pacing thresholds and sensing amplitudes. Data to support the effectiveness endpoints were measured at the MR Follow-up Visit prior to the MR scan and the Post-MR Follow-up Visit. Three separate consecutive sets of lead measurements were collected at these two visits to reliably determine if a chronic effect and permanent change was induced by the scan.

A summary of the effectiveness endpoints results are shown in Table 4. Details pertaining to each individual endpoint are provided in the following sections.

Table 4: Summary of Effectiveness Endpoint Results

Primary Effectiveness Endpoint	Assessment	One sided Alpha	Performance Result (Confidence Interval)	Performance Goal	Conclusion
RV Endpoint 1	Pacing Threshold - increase in pacing thresholds ≤ 0.5 V (at 0.5 ms)	5%	99.32% (96.79%)	87%	Endpoint Met
RV Endpoint 2	Sensed Amplitude – remains ≥ 5.0 mV and above 50% of the value at the MR Follow-up Visit	5%	99.32% (96.79%)	85%	Endpoint Met

Primary Effectiveness Endpoint	Assessment	One sided Alpha	Performance Result (Confidence Interval)	Performance Goal	Conclusion
LV Endpoint 1	Pacing Threshold - increase in pacing thresholds ≤ 1 V between MR Follow-up and Post-MR Follow-up Visits	5%	100.00% (97.53%)	87%	Endpoint Met
LV Endpoint 2	Sensed Amplitude – remains ≥ 5.0 mV and above 50% of the value at the MR Follow-up Visit	5%	98.31% (94.76%)	85%	Endpoint Met

<u>Primary RV Effectiveness Endpoint 1</u>: Pre-MR Scan vs. 1 Month Post-MR Scan RV Pacing Threshold at 0.5 ms

Multiple RV pacing threshold measurements taken at each of the two visits (MRI Visit and the MRI Visit + 1 Month; three separate consecutive sets of lead measurements requested) were averaged to determine the average RV pacing threshold at each visit for each subject. The change in average pacing thresholds was calculated for each subject and compared to 0.5 V to determine success or failure. Subjects that had an increase in average pacing thresholds (pre-MR Scan and at the MRI visit + 1 Month follow-up) ≤ 0.5 V were considered a success. The 95% one-sided lower pointwise confidence limit of the RV pacing threshold success rate was calculated using the one-sided exact methodology for a single binomial proportion and compared to the performance goal of 87%.

Primary RV Effectiveness Endpoint 1 was analyzed by per-protocol analysis. The per-protocol analysis only included subjects who received an MR Scan and had paired measurements for the MRI Visit and MRI + 1 Month Visit, and did not include subjects that met any of the following exclusions:

- Had a medically necessary scan between implant and the MRI + 1 Month Visit
- Failed to meet labeled MRI Conditions of Use
- Experienced a lead-related complication between MRI Visit and the MRI + 1 Month Visit
- Had an incomplete scan based on the ENABLE MRI Study MR Scan Sequences

A total of 146 subjects had paired threshold measurements and were included in the analysis. The success rate was 99.32% with a 95% one sided lower confidence limit (LCL) of 96.79%, which is greater than the performance goal of 87%.

This data supports the effectiveness of the ImageReady System with respect to stable RV pacing thresholds pre- and post-MR scan (a surrogate measurement for clinical effects of lead heating) when subjects are scanned according to the MRI Conditions of Use.

<u>Primary RV Effectiveness Endpoint 2:</u> Pre-MR Scan vs. 1 Month Post-MR Scan RV Sensed Amplitude

Multiple RV sensed amplitude measurements taken at each of the two visits (MRI Visit and the MRI Visit + 1 Month; three separate consecutive sets of lead measurements requested) were averaged to determine the average RV sensed amplitude at each visit for each subject. Subjects were considered a success if the average sensed amplitude at the MRI + 1 Month Visit remained ≥ 5.0 mV and above 50% of the pre-MR scan value. The percent of subjects meeting the success criteria was calculated. The 95% one-sided lower pointwise confidence limit of the RV sensed amplitude success rate was calculated using the one-sided exact methodology for a single binomial proportion and compared to the performance goal of 85%.

Primary RV Effectiveness Endpoint 2 was analyzed by per-protocol analysis. The per-protocol analysis only included subjects who received an MR Scan and had paired measurements for the MRI Visit and MRI + 1 Month Visit, and did not include subjects that met any of the following exclusions:

- Had a medically necessary scan between implant and the MRI + 1 Month Visit
- Failed to meet labeled MRI Conditions of Use
- Experienced a lead-related complication between MRI Visit and the MRI + 1 Month Visit
- Had an incomplete scan based on the ENABLE MRI Study MR Scan Sequences
- Average RV sensed amplitude < 5 mV pre-MR scan

A total of 146 subjects had paired sensed amplitude measurements and were included in the endpoint analysis. The success rate was 99.32% with a 95% one-sided lower confidence limit (LCL) of 96.79%, which is greater than the performance goal of 85%

This data supports the effectiveness of the ImageReady System with respect to stable RV sensed amplitude pre- and post-MR scan (a surrogate measurement for clinical effects of lead heating) when subjects are scanned according to the MRI Conditions of Use.

<u>Primary LV Effectiveness Endpoint 1:</u> Pre-MR scan vs. 1 Month Post-MR Scan LV Pacing Threshold at 0.5 ms

Multiple LV pacing threshold measurements taken at each of the two visits (MRI Visit and the MRI + 1 Month Visit; three consecutive sets of lead measurements requested) were averaged to determine the average LV pacing threshold at each visit for each subject. The change in average pacing thresholds was calculated for each subject and compared to 1.0 V to determine success or failure, and the percent of subjects meeting the success criteria was calculated. The 95% one-sided lower pointwise confidence limit of the LV pacing threshold success rate was calculated using the one-sided exact methodology for a single binomial proportion and compared to the performance goal of 87%.

Primary LV Effectiveness Endpoint 1 was analyzed by per-protocol analysis. The per-protocol analysis only included subjects who received an MR Scan and had paired measurements for the MRI Visit and MRI + 1 Month Visit, and did not include subjects that met any of the following exclusions:

- Had a medically necessary scan between implant and the MRI + 1 Month Visit
- Failed to meet labeled MRI Conditions of Use
- Experienced a lead-related complication between MRI Visit and the MRI + 1 Month Visit
- Had an incomplete scan based on the ENABLE MRI Study MR Scan Sequences

A total of 120 subjects had paired threshold measurements and were included in the analysis. The success rate was 100% with a 95% one sided lower confidence limit (LCL) of 97.53%, which exceeds the performance goal of 87%.

This data supports the effectiveness of the ImageReady System with respect to stable LV pacing thresholds pre- and post-MR scan (a surrogate measurement for clinical effects of lead heating) when subjects are scanned according to the MRI Conditions of Use.

Primary LV Effectiveness Endpoint 2: Pre-MR Scan vs. 1 Month Post-MR Scan LV Sensed Amplitude

Multiple LV sensed amplitude measurements taken at each of the two visits (MRI Visit and the MRI + 1 Month Visit; three separate consecutive set of lead measurements requested) were averaged to determine the average LV sensed amplitude at each visit for each subject. Subjects were considered a success if the average sensed amplitude at the MRI + 1 Month Visit remained ≥ 5.0 mV and above 50% of the average pre-MR Scan value. The percent of subjects meeting the success criteria was calculated. The 95% one-sided lower pointwise confidence limit of the LV sensed amplitude success rate was calculated using the one-sided exact methodology for a single binomial proportion and compared to the performance goal of 85%.

Primary LV Effectiveness Endpoint 2 was analyzed by per-protocol analysis. The per-protocol analysis only included subjects who received an MR Scan, had paired measurements for the MRI Visit and MRI + 1 Month Visit and did not include subjects that met any of the following exclusions:

- Had a medically necessary scan between implant and the MRI + 1 Month Visit
- Failed to meet labeled MRI Conditions of Use
- Experienced a lead-related complication between MRI Visit and the MRI + 1 Month Visit
- Had an incomplete scan based on the ENABLE MRI Study MR Scan Sequences
- Average LV sensed amplitude < 5 mV pre-MR scan

A total of 118 subjects had paired threshold measurements and were included in the analysis. The success rate was 98.31% with a 95% one sided lower confidence limit (LCL) of 94.76%, which is greater than the performance goal of 85%.

This data supports the effectiveness of the ImageReady System with respect to stable LV sensed amplitudes pre- and post-MR scan (a surrogate measurement for clinical effects of lead heating) when subjects are scanned according to the MRI Conditions of Use.

ADVERSE EVENTS SUMMARY

Table 5 summarizes the clinical events by category for the ENABLE MRI Study. A total of 155 events occurred in 79 subjects.

Table 5: Clinical Observations and Complications- All AEs
(N = 234 All PMA Cohort Attempted, Partial Implant or Implanted Subjects)

	Classification					
Classification	**Total**		**Complication**		**Observation**	
	Events	**N (%)**	**Events**	**N (%)**	**Events**	**N (%)**
Total (N at risk = 234)	155	79 (33.8%)	70	40 (17.1%)	85	60 (25.6%)
PG (N at risk = 234)	24	23 (9.8%)	2	2 (0.9%)	22	21 (9.0%)
RV Lead (N at risk = 234)	4	3 (1.3%)	4	3 (1.3%)	0	0 (0.0%)
LV Lead (N at risk = 195)	1	1 (0.5%)	1	1 (0.5%)	0	0 (0.0%)
Procedure (N at risk = 234)	11	10 (4.3%)	3	3 (1.3%)	8	7 (3.0%)
Cardiovascular - HF (N at risk = 234)	26	20 (8.5%)	13	11 (4.7%)	13	13 (5.6%)
Cardiovascular - Non-HF (N at risk = 234)	35	31 (13.2%)	9	9 (3.8%)	26	24 (10.3%)
Non-cardiovascular (N at risk = 234)	54	31 (13.2%)	38	21 (9.0%)	16	15 (6.4%)

DEATH SUMMARY

Table 6 provides an overview of subject deaths for the ENABLE MRI Study. There have been 5 deaths reported in the ENABLE MRI PMA population as of 28-Apr-2017.

No deaths were attributed to a MR scan.

Table 6: Summary of Subject Deaths
(N = 237 All Enrolled Subjects)

		MRI Related		System Related	
Cause of Death	**Classification N (%)**	**Yes N (%)**	**Unknown N (%)**	**Yes N (%)**	**Unknown N (%)**
Non cardiac	3 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
Unknown	2 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	5 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)

CONCLUSION

The results from the ENABLE MRI study confirm the safety and efficacy of the ImageReady MR Conditional Defibrillation System when used in accordance with the labeled MRI Conditions of Use.

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