Boston Scientific

CLINICAL SUMMARY

CAPTIVATE SUMMARY

CAPTure Information Via Automatic Threshold Evaluation

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 CAPTIVATE CLINICAL STUDY

1. Study Objectives

The CAPTIVATE study was designed to collect data to establish the safety and effectiveness of the AUTOGEN family of devices with the PaceSafe Right Ventricular Autothreshold (RVAT) and Left Ventricular Autothreshold (LVAT) features.

2. Study Design

CAPTIVATE was a prospective, non-randomized, multi-center, IDE clinical study.

The CAPTIVATE clinical study was conducted at 36 investigational centers in the USA and enrolled 216 subjects.

2.1. Study Subject Population

2.1.1. Inclusion Criteria

Subjects were included in the study if they met the following inclusion criteria.

Table 2.1-1: Inclusion Criteria

• Subjects prescribed a CRT-D and indicated per guidelines, who will receive an AUTOGEN CRT-D model G160, G161, G172, G173 • Subjects who have an implanted functional endocardial right ventricular defibrillation lead or who will receive a endocardial right ventricular defibrillation lead • Subjects who have an implanted functional bipolar or unipolar left ventricular lead or who will receive a bipolar or unipolar left ventricular lead • Subjects who are willing and capable of providing informed consent to undergo a device implant procedure, and to participate in all testing and follow-ups defined in this protocol • Subjects whose age is 18 or above, or of legal age to give informed consent specific to national law
Abbreviations: CRT-D= Cardiac Resynchronization Therapy – Defibrillator Source: Clinical Investigational Plan

2.1.2. Exclusion Criteria

Exclusion Criteria Subjects were ineligible to participate in the study if they met the following exclusion criteria.

Table 2.1-2: Exclusion Criteria

- Subjects who have an implanted multipolar (>2poles) left ventricular lead or who will receive a multipolar (>2poles) left ventricular lead
- Subjects with an unknown model/manufacturer, or implant date for the RA, RV or LV lead
- Subjects for whom a RV defibrillation lead manufactured by St. Jude Medical or Biotronik is implanted, is planned to be implanted, or has been abandoned
- Implanted with an active Medtronic Sprint Fidelis® lead models: 6930, 6931, 6948 or 6949
- Subjects with an implanted or abandoned St. Jude Medical QuickSite® or QuickFlex® lead models: 1056T, 1058T, 1156T, 1158T
- Subjects with a RV or LV lead revision or extraction within 30 days of enrollment
- Subjects with an implanted lead that is planned to be extracted during the study implant procedure
- Subjects with an active implanted RA or RV lead that is greater than 10 years old, unless the lead will be abandoned
- Subjects with an active implanted LV lead that is greater than 8 years old, unless the lead will be abandoned
- Subjects preexisting unipolar pacemaker that will not be explanted/abandoned
- Subjects with a life expectancy less than 6 months
- Subjects with a prosthetic mechanical tricuspid heart valve
- Women of childbearing age who are pregnant or plan to become pregnant
- Subject enrolled in a concurrent study, except national/governmental registries that do not require a signed informed consent form, without the written approval from Boston Scientific
- Subjects who are not geographically stable, to the extent that it would prevent attending the study follow-ups at the investigational center

Abbreviations: RA: Right Atrium; RV: Right Ventricle; LV: Left Ventricle

Source: Clinical Investigational Plan

3. Endpoints

3.1. Primary Safety Endpoint: System-Related Complicate Free Rate

Safety of the AUTOGEN CRT-Ds was evaluated by the system-related complication-free rate (CFR) at 3-months post-implant. The system consists of the implanted AUTOGEN CRT-D pulse generator, RA lead (if implanted), RV lead, and LV lead.

3.2. RVAT Primary Efficacy 1: Accuracy of the Commanded RVAT

The accuracy of the RVAT commanded test was evaluated by comparing the RVAT determined threshold to a core lab (independent physician) determined threshold. The primary efficacy endpoint evaluated the proportion of tests resulting in an accurate RVAT commanded threshold at the 1-month and 3-month follow-up visits.

3.3. LVAT Primary Efficacy Endpoint 1: Accuracy of the Commanded LVAT

The accuracy of the LVAT commanded test was evaluated by comparing the LVAT determined threshold to a core lab (independent physician) determined threshold. The primary efficacy endpoint evaluated the proportion of tests resulting in an accurate LVAT commanded threshold at the 1-month and 3-month follow-up visits.

3.4. RVAT Primary Efficacy Endpoint 2: Accuracy of the Ambulatory RVAT

The accuracy of the RVAT ambulatory test was evaluated by comparing the core lab determined manual RV threshold from the real-time ECG during the manual test to the most recent RVAT ambulatory test value stored in the device that occurred within the previous 7 days. The primary effectiveness endpoint 2 evaluated the proportion of tests resulting in an accurate ambulatory threshold at the 1-month and the 3-month follow-up visits.

3.5. LVAT Primary Efficacy Endpoint 2: Accuracy of the Ambulatory LVAT

The accuracy of the LVAT ambulatory test was evaluated by comparing the core lab determined manual LV threshold from the real-time ECG during the manual test to the most recent LVAT ambulatory test value stored in the device that occurred within the previous 7 days. The primary efficacy endpoint 2 evaluated the proportion of tests resulting in an accurate ambulatory threshold at the 1-month and the 3-month follow-up visits.

3.6. RVAT Secondary Efficacy Endpoint: RVAT Appropriate Test Outcome

This endpoint evaluated the percent of RVAT commanded tests that resulted in an appropriate outcome.

3.7. LVAT Secondary Efficacy Endpoint: LVAT Appropriate Test Outcome

This endpoint evaluated the percent of LVAT commanded tests that resulted in an appropriate outcome.

4. Results

4.1. Subject Disposition

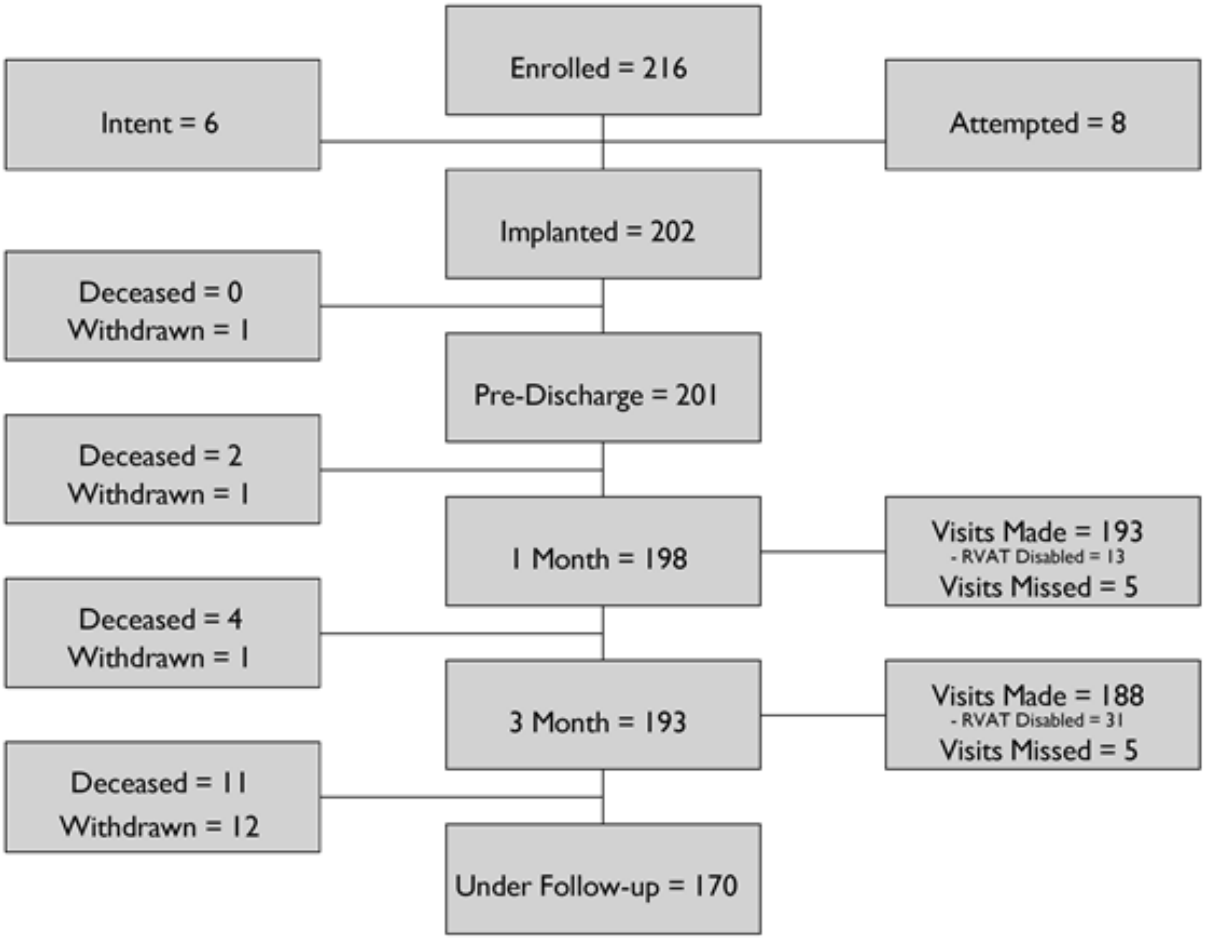


Figure 4.1-1: Subject Disposition

4.2. Subject Demographics

Below is a table summarizing the baseline patient demographics and clinical characteristics.

Table 4.2-1: Patient Demographics and Clinical Characteristics

Characteristic	Measurement	Result
Age at Implant (years)	N	210
	Mean ± SD	69.8 ± 10.8
	Range	28.0 - 93.0
Gender [N (%)]	Male	140 (67)
	Female	70 (33)
NYHA Class [N (%)]	Class I	2 (1)
	Class II	54 (26)

Characteristic	Measurement	Result
	Class III	146 (70)
	Class IV	6 (3)
	Not Available	2 (1)
LVEF (%)	N	209
	Mean ± SD	26.8 ± 8.1
	Range	10.0 - 70.0
QRS Duration (ms)	N	208
	Mean ± SD	157 ± 24
	Range	90 - 248
PR Interval (ms)	N	159
	Mean ± SD	190 ± 44
	Range	80 - 352
Pulse (bpm)	N	210
	Mean ± SD	73 ± 15
	Range	35 - 115
Height (cm)	N	210
	Mean ± SD	172 ± 10
	Range	150 - 198
Weight (kg)	N	210
	Mean ± SD	90 ± 23
	Range	45 - 176
Body Mass Index (kg/m2)	N	210
	Mean ± SD	30.4 ± 7.2
	Range	17.7 - 56.0
Systolic Blood Pressure (mmHg)	N	210
	Mean ± SD	126 ± 20
	Range	80 - 177
Diastolic Blood Pressure (mmHg)	N	210
	Mean ± SD	71 ± 13
	Range	40 - 108
Concomitant Medications* [N (%)]	ACE Inhibitor	128 (61)
	Angiotensin Receptor Blocker (ARB)	44 (21)
	Antiarrhythmic Drugs	34 (16)
	Beta Blockers (Class II)	171 (81)
	Digoxin	22 (10)
	Diuretics	159 (76)
Conduction Disorder [N (%)]	Left Bundle Branch Block	140 (67)
	Other	38 (18)
	None	19 (9)
	Right Bundle Branch Block	13 (6)
Primary Attrial Arrhythmia [N (%)]	Atrial Fibrillation	69 (33)

Characteristic	Measurement	Result
	Other	8 (4)
	Atrial Flutter	6 (3)
	Sinus Node Dysfunction	6 (3)
	Sick Sinus Syndrome	4 (2)
	Paroxysmal Atrial Tachycardia	3 (1)
	PSVT	1 (0)
	None	113 (54)
Primary Tachy Arrhythmia [N (%)]	Other	33 (16)
	Nonsustained VT	21 (10)
	Premature Ventricular Contractions	12 (6)
	Monomorphic VT	3 (1)
	Nonsustained VT with inducible MVT	2 (1)
	Ventricular Flutter	1 (0)
	None	138 (66)
Cardiac Disease History* [N (%)]	Dilated Cardiomyopathy	46 (22)
	Ischemic Cardiomyopathy	104 (50)
	Non-ischemic Cardiomyopathy	94 (45)
	Previous Myocardial Infarction (MI)	59 (28)
	Primary Valvular Cardiomyopathy	8 (4)
Comorbidities* [N (%)]	Hyperlipidemia	155 (74)
	Hypertension	170 (82)
	Renal Dysfunction	51 (25)
	Type I Diabetes	7 (3)
	Type II Diabetes	91 (45)
	Anemia	30 (15)
	History of TIA or stroke	28 (14)
	COPD	43 (22)
	Peripheral Vascular Disease	34 (17)
	Hepatic Disease	4 (2)
	Pulmonary Hypertension Primary	18 (9)
	Asthma	14 (7)
	Sleep Disordered Breathing	40 (21)
	Pulmonary Hypertension Secondary	10 (5)
HF Signs* [N (%)]	Edema	70 (34)
	Pulmonary Rales	6 (3)
	Heart Sounds Audible S3	15 (8)
	Heart Sounds Audible S4	8 (4)
	Liver Tenderness	0 (0)
	Mitral Regurgitation	87 (44)
	Jugular Venous Distention (JVD)	14 (7)
	Hepatomegaly	0 (0)
	Ascites	1 (1)

Characteristic	Measurement	Result
HF Symptoms* [N (%)]	Dyspnea during exertion	174 (85)
	Orthopnea	39 (20)
	Paroxysmal Nocturnal Dyspnea (PND)	28 (14)
	Fatigue	147 (77)
	Dyspnea at rest	45 (25)
	Nocturnal Cough	13 (7)
* Patients may contribute to more than one category		

4.3. Study Endpoint Analyses

Table 4.3-1: CAPTIVATE Study Results

	Endpoint	Assessment	Expected Value	Performance Goal	Result	Conclusion
Efficacy	RVAT Primary 1	Percent of Commanded RVAT Tests that resulted in an Accurate Threshold	95%	90%	% (LCL) = 97.9% (95.9%)	Pass
	RVAT Primary 2	Percent of Ambulatory RVAT Tests that resulted in an Accurate Threshold	96.5%	90%	% (LCL) = 99.0% (97.5%)	Pass
	RVAT Secondary	Percent of RVAT Commanded Tests that resulted in an Appropriate Outcome	80%	70%	% (LCL) = 86.9% (83.5%)	Pass
	LVAT Primary 1	Percent of Commanded LVAT Tests that resulted in an Accurate Threshold	95%	90%	% (LCL) = 97.8% (96.0%)	Pass
	LVAT Primary 2	Percent of Ambulatory LVAT Tests that resulted in an Accurate Threshold	96.5%	90%	% (LCL) = 97.7% (95.7%)	Pass
	LVAT Secondary	Percent of LVAT Commanded Tests that resulted in an Appropriate Outcome	80%	70%	% (LCL) = 95.4% (93.2%)	Pass
Safety	Primary	3 Month Post-Implant System-Related Complication-Free Rate	80%	70%	% (LCL) = 84.2% (79.5%)	Pass

4.3.1. Primary Safety Endpoint Results: System-Related Complication-Free Rate

The objective of this endpoint was to evaluate and document the safety of the AUTOGEN system by assessing the system-related complication-free rate for subjects through 3 months post-

implant. The system consists of the implanted AUTOGEN CRT-D pulse generator, RA lead, RV lead, and LV lead.

4.3.1.1. Hypothesis

The primary safety endpoint is to demonstrate that the system-related complication-free rate through the patient's 3-month follow-up period is greater than the specified performance goal.

H0: The three month system-related complication-free rate < 70%, and

H1: The three month system-related complication-free rate > 70%

4.3.1.2. Results

The 3-month system-related complication-free rate was 84.2% with a one-sided lower 95% confidence limit of 79.5%. The lower confidence limit is greater than the performance goal of 70%, resulting in a rejection of the null hypothesis.The results can be found in Figure 4.3-1.

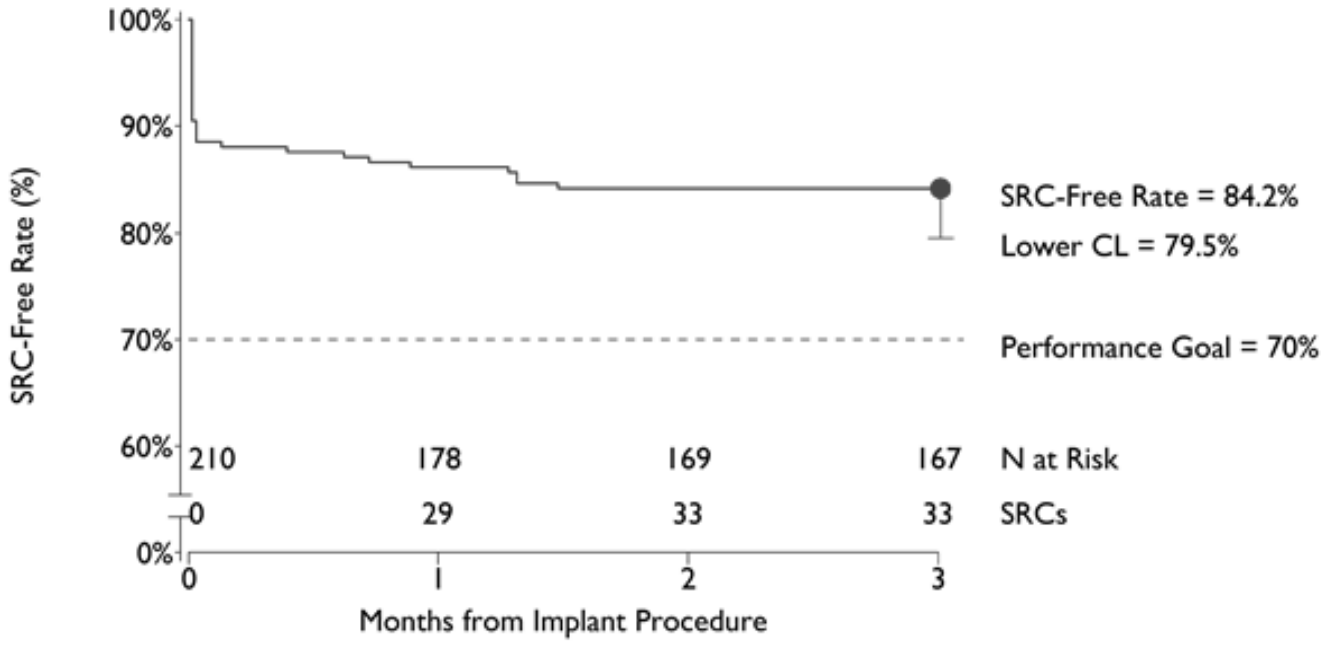


Figure 4.3-1: Primary Safety Endpoint Results - System-related Complication-Free Rate through 3 Months

Table 4.3-2 presents a breakdown of the system-related complications that contributed to the Primary Safety Endpoint. None of the system-related complications through three months were related to the RVAT or LVAT algorithms. The results are presented in descending frequency of system-related complication.

Table 4.3-2: Breakdown of System-Related Complication-Free Rates through 3 Months

System-Related Complication	System- Related Complications (SRCs)	SRC-Free Rate	95% One-Sided Lower CL
Dislodgment (LV Lead)	7	96.6%	93.7%
Extracardiac Stimulation (LV Lead)	6	97.1%	94.4%
Dislodgment (RV Lead)	3	98.5%	96.2%
Pneumothorax (Procedure)	3	98.6%	96.3%
Adverse Reaction - Hypotension (Procedure)	2	99.0%	97.0%
Hematoma - Pocket (<=30 Days Post-Implant) (Procedure)	2	99.0%	96.9%
Other-Lead-Procedure (Procedure)	2	99.0%	97.0%
Unable To Capture (LV Lead)	2	99.0%	97.0%
Adverse Reaction - Respiratory (Procedure)	1	99.5%	97.5%
Dislodgment (RA Lead)	1	99.5%	97.6%
Dyspnea - Heart Failure (Cardiovascular - HF)	1	99.5%	97.5%
Failure To Implant Epicardial LV Lead (Procedure)	1	99.5%	97.6%
Inability To Place The LV Lead (Procedure)	1	99.5%	97.6%
Inappropriate Tachy Therapy - SVT (PG)	1	99.5%	97.4%
Insulation Breach (RV Lead)	1	99.5%	97.6%
Myocardial Perforation Post-Implant (RV Lead)	1	99.5%	97.6%
Myocardial Perforation With Tamponade (Procedure)	1	99.5%	97.6%
Pericardial Effusion (Procedure)	1	99.5%	97.6%
Post-Surgical Pocket Hemorrhage (Procedure)	1	99.5%	97.5%
Post-Surgical Wound Discomfort (Procedure)	1	99.5%	97.5%
Renal Failure Due To Contrast Media (Procedure)	1	99.5%	97.5%
Unable To Capture (PG)	1	99.5%	97.5%
Unable To Convert - Defibrillation (PG)	1	99.5%	97.6%
Unable To Insert LV Lead With Initial Procedure (Procedure)	1	99.5%	97.6%
Total	**33**	**84.2%**	**79.5%**

4.3.1.3. Conclusion

The 3-month system-related complication-free rate was 84.2% with a one-sided lower 95% confidence limit of 79.5%, which was greater than the performance goal of 70%. The data support the safety of the AUTOGEN system.

4.3.2. RVAT Primary Efficacy Endpoint 1: Accuracy of the Commanded RVAT

The objective of this endpoint was to demonstrate the clinical equivalence of the commanded thresholds determined by the RVAT algorithm and the thresholds determined from the real-time ECG collected during the Commanded autothreshold tests, as evaluated by the core lab.

4.3.2.1. Hypotheses

The primary efficacy endpoint is to demonstrate the accuracy of RV thresholds determined by a Commanded RVAT test vs. a core lab determined threshold at the 1-month and 3-month follow-up visits. This endpoint will be evaluated by determining the percent of accurate paired threshold tests:

H0: The proportion of tests with accurate RVAT commanded threshold ≤ 90%

H1: The proportion of tests with accurate RVAT commanded threshold > 90%

Where an accurate commanded threshold is defined by:

|commanded threshold – core lab determined threshold| ≤ 0.2V; if the commanded threshold is ≤ 3.5V

or

|commanded threshold – core lab determined threshold| ≤ 0.5V; if the commanded threshold is > 3.5V

4.3.2.2. Data Analysis

The primary efficacy endpoint evaluated the proportion of tests resulting in an accurate RVAT commanded threshold at the 1-month and 3-month follow-up visits. Subjects were allowed to contribute multiple paired datasets for this endpoint analysis, one set each from the 1-month and 3-month visits.

The proportion of accurate commanded threshold tests was calculated and the corresponding lower one-sided 95% Clopper-Pearson confidence limit of the proportion was compared to the performance goal of 90%.

4.3.2.3. Results

A total of 288 paired datasets (in 171 unique subjects), each consisting of a commanded RVAT threshold and a core lab determined threshold, were collected at the1-month and 3-month visits. Of those 288 commanded RVAT thresholds, 282 (97.9%) resulted in an accurate threshold. The corresponding 95% one-sided lower confidence limit of 95.9% was greater than the performance goal of 90% ($p < 0.001$), resulting in a rejection of the null hypothesis.

Additionally, 90.6% of RVAT thresholds were identical to the core lab determined thresholds, providing further evidence of the accuracy of the RVAT feature.

Results by 1-month and 3-month visit are shown in Figure 4.3-2.

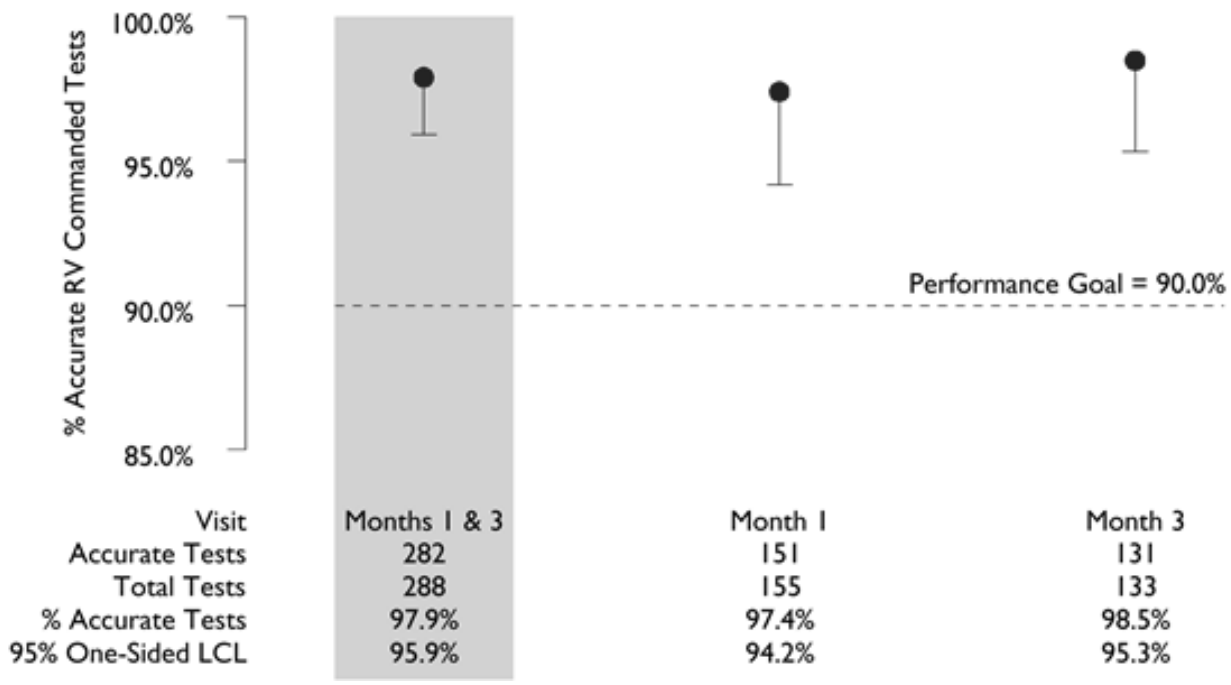


Figure 4.3-2: Primary Effectiveness Endpoint 1 Results – Accurate Commanded RVAT Thresholds

4.3.2.4. Conclusion

The RVAT commanded threshold test produced an accurate threshold in 97.9% of tests in which a threshold was obtained. The corresponding 95% one-sided lower confidence limit of 95.9% was greater than the performance goal of 90%, therefore the data support the accuracy and the effectiveness of the RVAT commanded feature.

4.3.3. RVAT Primary Efficacy Endpoint 2: Accuracy of the Ambulatory RVAT

The objective of this endpoint was to demonstrate the clinical equivalence of the ambulatory thresholds determined by the RVAT algorithm and the core lab determined manual RV threshold from the real-time ECG obtained during the manual test.

4.3.3.1. Hypotheses

The RVAT primary efficacy endpoint 2 is to demonstrate the accuracy of RV thresholds determined by an Ambulatory RVAT test vs. a core lab determined threshold at the 1-month and 3-month follow-up visits. This endpoint will be evaluated by determining the percent of accurate paired threshold tests:

H0: The proportion of accurate ambulatory tests ≤ 90%

H1: The proportion of accurate ambulatory tests > 90%

Where an accurate Ambulatory threshold is defined by:

|Ambulatory threshold – ECG threshold| ≤ 0.6V; if the ECG threshold is ≤ 3.5V

or

|Ambulatory threshold – ECG threshold| ≤ 1.0V; if the ECG threshold is > 3.5V

4.3.3.2. Data Analysis

The primary effectiveness endpoint 2 evaluated the proportion of tests resulting in an accurate ambulatory threshold at the 1-month and the 3-month follow-up visits. Subjects were allowed to contribute multiple paired datasets for this endpoint analysis, one set each from the 1-month and 3-month visits.

The proportion of accurate ambulatory threshold tests was calculated, and the corresponding lower one-sided 95% Clopper-Pearson confidence limit of the proportion was compared to the performance goal of 90%.

4.3.3.3. Results

A total of 314 paired datasets (in 183 unique subjects), each consisting of an ambulatory RVAT threshold and core lab determined threshold, were collected at the 1-month and 3-month visits. Of the 314 RVAT ambulatory threshold tests, 311 (99.0%) resulted in an accurate threshold. The corresponding 95% one-sided lower confidence limit of 97.5% was greater than the performance goal of 90% ($p < 0.001$), resulting in a rejection of the null hypothesis.

Additionally, 91.5% of RVAT ambulatory thresholds were within 0.1V of the core lab determined thresholds.

Results by 1-month and 3-month visit are shown in Figure 4.3-3 with 99.4% of RVAT ambulatory threshold tests at the 1-month visit and 98.7% at the 3-month visit resulting in an accurate threshold.

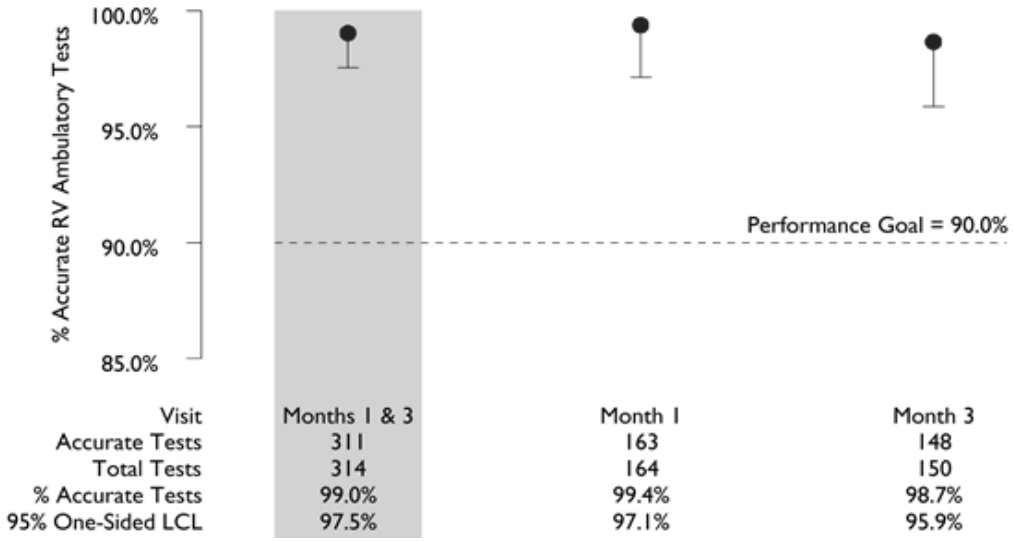


Figure 4.3-3: Primary Effectiveness Endpoint 2 – Accurate Ambulatory RVAT Thresholds

4.3.3.4. Conclusion

The RVAT ambulatory threshold test produced an accurate threshold in 99.0% of tests in which a threshold was obtained. The corresponding 95% one-sided lower confidence limit of 97.5% was greater than the performance goal of 90%, therefore the data support the accuracy and the effectiveness of the RVAT ambulatory feature.

4.3.4. RVAT Secondary Efficacy Endpoint: RVAT Appropriate Test Outcome

The objective of this endpoint was to demonstrate that the commanded RVAT threshold test produces appropriate outcomes. There are three possible outcomes to a commanded test:

1. A device-determined threshold
2. A threshold test code (indicating that a threshold could not be determined) representing an error condition that is beyond the control of the RVAT feature and could occur in the manual threshold tests
3. A threshold test code (indicating that a threshold could not be determined) that was due to a limitation of the RVAT feature and might not occur in manual threshold tests

An appropriate RVAT outcome consists of the first two outcomes listed above: a device-determined threshold and a threshold test code representing an error condition that is beyond the control of the RVAT feature and could occur in the manual threshold tests. An inappropriate RVAT outcome consists of the last of the three outcomes listed above.

4.3.4.1. Hypotheses

The secondary RVAT efficacy endpoint is to demonstrate how often the commanded RVAT test results in an appropriate test outcome.

H0: The proportion of commanded tests that result in an appropriate outcome ≤ 70%

H1: The proportion of commanded tests that result in an appropriate outcome > 70%

4.3.4.2. Data Analysis

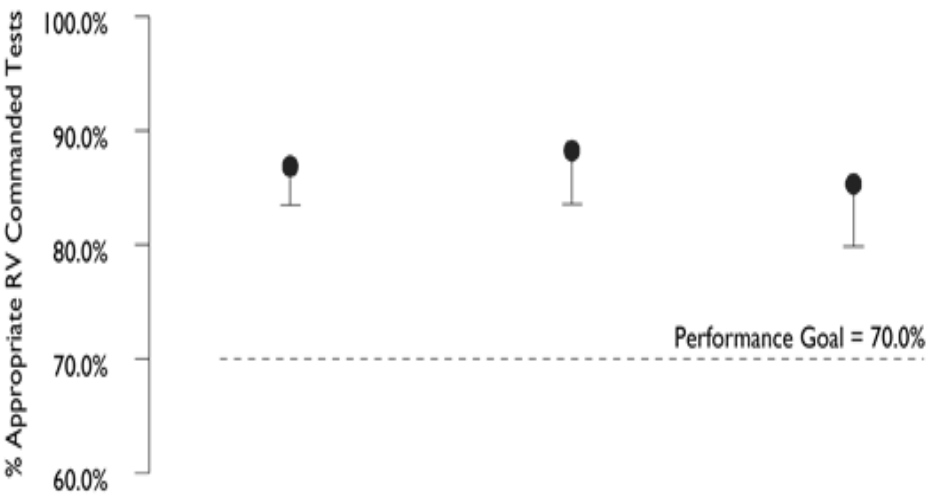
The RVAT secondary efficacy endpoint evaluated the proportion of Commanded RVAT tests resulting in an appropriate outcome at the 3-month follow-up visit. All attempted Commanded RVAT tests from the 3-month visit were included in the analysis.

The one-sided exact binomial test was used to test the hypothesis that the rate of appropriate RVAT outcomes is greater than the performance goal of 70%. If the lower one-sided Clopper-Pearson 95% confidence limit for the proportion of tests with an appropriate RVAT test outcome was greater than 70% then the null hypothesis was rejected in favor of the alternative.

4.3.4.3. Results

There were a total of 157 tests collected at the 3-month visit with 134 (85.4%) resulting in an appropriate test outcome. The corresponding 95% one-sided lower confidence limit of 79.9% was greater than the performance goal of 70% ($p < 0.001$), resulting in a rejection of the null hypothesis.

It was pre-specified that the 3-month visit data would be used for the secondary efficacy endpoint. Data from the 1-month visit and 1-month and 3-month pooled data are also presented in Figure 4.3-4.



Visit	Months 1 & 3	Month 1	Month 3
Appropriate Tests	292	158	134
Total Tests	336	179	157
% Appropriate Tests	86.9%	88.3%	85.4%
95% One-Sided LCL	83.5%	83.5%	79.9%

Figure 4.3-4: Secondary Effectiveness Endpoint – Appropriate Commanded RVAT Tests

4.3.4.4. Conclusion

RVAT commanded tests resulted in an appropriate outcome in 85.4% of attempted tests at the 3-month visit (95% one-sided lower confidence limit of 79.9%). This exceeded the performance goal and supports the effectiveness of the RVAT commanded feature in producing an appropriate test outcome.

4.3.5. LVAT Primary Efficacy Endpoint 1: Accuracy of the Commanded LVAT

The objective of this endpoint was to demonstrate the clinical equivalence of the commanded thresholds determined by the LVAT algorithm and the thresholds determined from the real-time ECG collected during the Commanded autothreshold tests, as evaluated by the core lab.

4.3.5.1. Hypothesis

The primary efficacy endpoint is to demonstrate the accuracy of LV thresholds determined by a Commanded LVAT test vs. a core lab determined threshold at the 1-month and 3-month follow-up visits. This endpoint will be evaluated by determining the percent of accurate paired threshold tests:

H0: The proportion of tests with accurate LVAT commanded threshold ≤ 90%

H1: The proportion of tests with accurate LVAT commanded threshold > 90%

Where an accurate commanded threshold is defined by:

|commanded threshold – core lab determined threshold| ≤ 0.2V; if the commanded threshold is ≤ 3.5V

or

|commanded threshold – core lab determined threshold| ≤ 0.5V; if the commanded threshold is > 3.5V

4.3.5.2. Data Analysis

The primary efficacy endpoint evaluated the proportion of tests resulting in an accurate LVAT commanded threshold at the 1-month and 3-month follow-up visits. Subjects were allowed to contribute multiple paired datasets for this endpoint analysis, one set each from the 1-month and 3-month visits.

The proportion of accurate commanded threshold tests was calculated, and the corresponding lower one-sided 95% Clopper-Pearson confidence limit of the proportion was compared to the performance goal of 90%.

4.3.5.3. Results

A total of 324 paired datasets (in 182 unique subjects), each consisting of a commanded LVAT threshold and a core lab determined threshold, were collected at the 1-month and 3-month visits. Of those 324 commanded LVAT thresholds, 317 (97.8%) resulted in an accurate threshold. The corresponding 95% one-sided lower confidence limit of 96.0% was greater than the performance goal of 90% (p <0.001), resulting in a rejection of the null hypothesis.

Additionally, 96.6% of LVAT thresholds were within 0.1V of the core lab determined threshold, providing further evidence of the accuracy of the LVAT feature.

Results by 1-month and 3-month visit are shown in Figure 4.3-5.

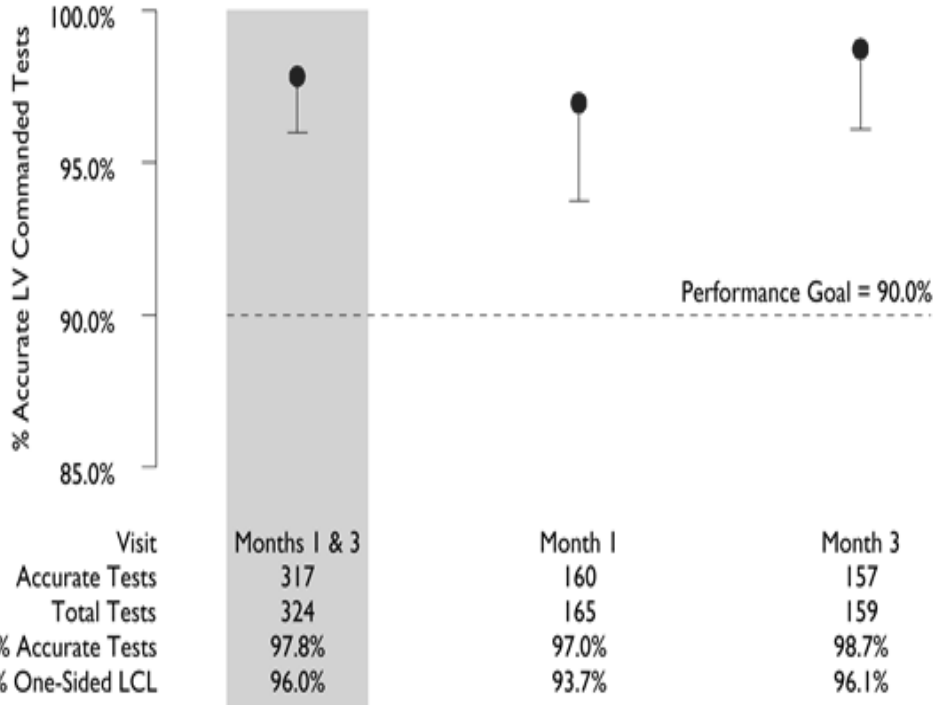


Figure 4.3-5: Primary Effectiveness Endpoint 1 Results – Accurate Commanded LVAT Thresholds

4.3.5.4. Conclusion

The LVAT commanded threshold test produced an accurate threshold in 97.8% of tests in which a threshold was obtained. The corresponding 95% one-sided lower confidence limit of 96.0% was greater than the performance goal of 90%, therefore the data support the accuracy and the effectiveness of the LVAT commanded feature.

4.3.6. LVAT Primary Efficacy Endpoint 2: Accuracy of the Ambulatory LVAT

The objective of this endpoint was to demonstrate the clinical equivalence of the ambulatory thresholds determined by the LVAT algorithm and the core lab determined manual LV threshold from the real-time ECG obtained during the manual test.

4.3.6.1. Hypotheses

The LVAT primary efficacy endpoint 2 is to demonstrate the accuracy of LV thresholds determined by an Ambulatory LVAT test vs. a core lab determined threshold at the 1-month and 3-month follow-up visits. This endpoint will be evaluated by determining the percent of accurate paired threshold tests:

H0: The proportion of accurate ambulatory tests ≤ 90%

H1: The proportion of accurate ambulatory tests > 90%

Where an accurate Ambulatory threshold is defined by:

|Ambulatory threshold – ECG threshold| ≤ 1.0V

4.3.6.2. Data Analysis

The primary efficacy endpoint 2 evaluated the proportion of tests resulting in an accurate ambulatory threshold at the 1-month and the 3-month follow-up visits. Subjects were allowed to contribute multiple paired datasets for this endpoint analysis, one set each from the 1-month and 3-month visits.

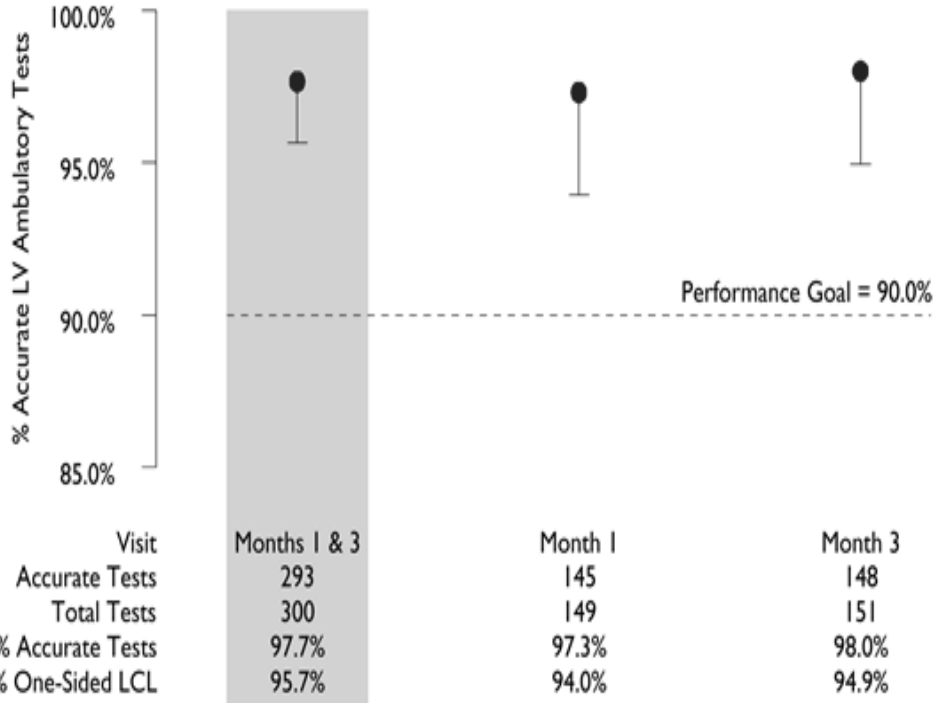
The proportion of accurate ambulatory threshold tests was calculated, and the corresponding lower one-sided 95% Clopper-Pearson confidence limit of the proportion was compared to the performance goal of 90%.

4.3.6.3. Results

A total of 300 paired datasets (in 175 unique subjects), each consisting of an ambulatory LVAT threshold and core lab determined threshold, were collected at the 1-month and 3-month visits. Of the 300 LVAT ambulatory threshold tests, 293 (97.7%) resulted in an accurate threshold. The corresponding 95% one-sided lower confidence limit of 95.7% was greater than the performance goal of 90% ($p < 0.001$), resulting in a rejection of the null hypothesis.

Additionally, 95.0% of LVAT ambulatory thresholds were within 0.5V of the core lab determined thresholds.

Results by 1-month and 3-month visit are shown in Figure 4.3-6 with 97.3% of LVAT ambulatory threshold tests at the 1-month visit and 98.0% at the 3-month visit resulting in an accurate threshold.



Visit	Months 1 & 3	Month 1	Month 3
Accurate Tests	293	145	148
Total Tests	300	149	151
% Accurate Tests	97.7%	97.3%	98.0%
95% One-Sided LCL	95.7%	94.0%	94.9%

Figure 4.3-6: Primary Effectiveness Endpoint 2 – Accurate Ambulatory LVAT Thresholds

4.3.6.4. Conclusion

The LVAT ambulatory threshold test produced an accurate threshold in 97.4% of tests in which a threshold was obtained. The corresponding 95% one-sided lower confidence limit of 95.7% was greater than the performance goal of 90%, therefore the data support the accuracy and the effectiveness of the LVAT ambulatory feature.

4.3.7. LVAT Secondary Efficacy Endpoint: LVAT Appropriate Test Outcome

The objective of this endpoint was to demonstrate that the commanded LVAT threshold test produces appropriate outcomes. There are three possible outcomes to a commanded test:

1. A device-determined threshold
2. A threshold test code (indicating that a threshold could not be determined) representing an error condition that is beyond the control of the LVAT feature and could occur in the manual threshold tests
3. A threshold test code (indicating that a threshold could not be determined) that was due to a limitation of the LVAT feature and might not occur in manual threshold tests

An appropriate LVAT outcome consists of the first two outcomes listed above: a device-determined threshold and a threshold test code representing an error condition that is beyond the control of the LVAT feature and could occur in the manual threshold tests. An inappropriate LVAT outcome consists of the last of the three outcomes listed above.

4.3.7.1. Hypotheses

The secondary LVAT efficacy endpoint is to demonstrate how often the commanded LVAT test results in an appropriate test outcome.

H0: The proportion of commanded tests that result in an appropriate outcome ≤ 70%

H1: The proportion of commanded tests that result in an appropriate outcome > 70%

4.3.7.2. Data Analysis

The LVAT secondary efficacy endpoint evaluated the proportion of Commanded LVAT tests resulting in an appropriate outcome at the 3-month follow-up visit. All attempted Commanded LVAT tests from the 3-month visit were included in the analysis.

The one-sided exact binomial test was used to test the hypothesis that the rate of appropriate LVAT outcomes is greater than the performance goal of 70%. If the lower one-sided Clopper-Pearson 95% confidence limit for the proportion of tests with an appropriate LVAT test outcome was greater than 70% then the null hypothesis was rejected in favor of the alternative.

4.3.7.3. Results

There were a total of 182 tests collected at the 3-month visit with 173 (95.1%) resulting in an appropriate test outcome. The corresponding 95% one-sided lower confidence limit of 91.5% was greater than the performance goal of 70% (p <0.001), resulting in rejection of the null hypothesis.

It was pre-specified that the 3-month visit data would be used for the secondary efficacy endpoint. Data from the 1-month visit and 1-month and 3-month pooled data are also presented in Figure 4.3-7.

Visit	Months 1 & 3	Month 1	Month 3
Appropriate Tests	353	180	173
Total Tests	370	188	182
% Appropriate Tests	95.4%	95.7%	95.1%
95% One-Sided LCL	93.2%	92.5%	91.5%

Figure 4.3-7: Secondary Effectiveness Endpoint – Appropriate Commanded LVAT Tests

4.3.7.4. Conclusion

LVAT commanded tests resulted in an appropriate outcome in 95.1% of attempted tests at the 3-month visit (95% one-sided lower confidence limit of 91.5%). This exceeded the performance goal and supports the effectiveness of the LVAT commanded feature in producing an appropriate test outcome.

4.4. Summary of Adverse Events

The data in the Adverse Events Summary table is complete as of May 23, 2016.

Table 4.4-1: Clinical Observations and Complications Summary

All subjects implanted or attempted, n=208

		Complications		Observations	
Adverse Event	**Total Events (N Subjects)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
Total Adverse Events	544 (160)	288	114 (54.3)	245	109 (51.9)
PG Related Events (N at risk = 202)					
Cannot Do RV Threshold Test	1 (1)	0	0 (0.0)	1	1 (0.5)
Elevated Threshold - LV	1 (1)	1	1 (0.5)	0	0 (0.0)
Inappropriate Tachy Therapy - SVT	2 (2)	2	2 (1.0)	0	0 (0.0)
Infection (> 3 Days Post-Implant)	1 (1)	1	1 (0.5)	0	0 (0.0)
Migration	1 (1)	1	1 (0.5)	0	0 (0.0)
Oversensing - RV	1 (1)	0	0 (0.0)	1	1 (0.5)
Pacemaker-Mediated Tachycardia (PMT)	8 (8)	0	0 (0.0)	8	8 (4.0)
PG System - Patient Related	1 (1)	0	0 (0.0)	1	1 (0.5)
Psychological Effect Due To Device Therapy	2 (2)	0	0 (0.0)	2	2 (1.0)
Unable To Capture - LV	1 (1)	1	1 (0.5)	0	0 (0.0)
Unable To Convert - Defibrillation	1 (1)	1	1 (0.5)	0	0 (0.0)
Undersensing - RA	1 (1)	0	0 (0.0)	1	1 (0.5)
Subtotal PG Related Events	**21 (21)**	**7**	**7 (3.5)**	**14**	**14 (6.9)**
RA Lead Related Events (N at risk =192)					
Dislodgment - Extracardiac Stimulation - RA	1 (1)	0	0 (0.0)	1	1 (0.5)
Dislodgment - No Reported Signs - RA	1 (1)	1	1 (0.5)	0	0 (0.0)
Dislodgment - Unable To Capture - RA	1 (1)	1	1 (0.5)	0	0 (0.0)
Impedance < 300 Ohms - RA	1 (1)	1	1 (0.5)	0	0 (0.0)
Subtotal RA Lead Related Events	**4 (4)**	**3**	**3 (1.6)**	**1**	**1 (0.5)**
RV Lead Related Events (N at risk =202)					
Dislodgment - Elevated Threshold - RV	1 (1)	1	1 (0.5)	0	0 (0.0)
Dislodgment - Multiple Signs - RV	2 (1)	2	1 (0.5)	0	0 (0.0)
Dislodgment - Unable To Capture - RV	1 (1)	1	1 (0.5)	0	0 (0.0)
Insulation Breach - RV	1 (1)	1	1 (0.5)	0	0 (0.0)
Myocardial Perforation Post-Implant - RV	1 (1)	1	1 (0.5)	0	0 (0.0)
Subtotal RV Lead Related Events	**6 (5)**	**6**	**5 (2.5)**	**0**	**0 (0.0)**

		Complications		Observations	
Adverse Event	**Total Events (N Subjects)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
LV Lead Related Events (N at risk =202)					
Dislodgment - Extracardiac Stimulation - LV	1 (1)	1	1 (0.5)	0	0 (0.0)
Dislodgment - No Reported Signs - LV	4 (4)	4	4 (2.0)	0	0 (0.0)
Dislodgment - Unable To Capture - LV	4 (4)	4	4 (2.0)	0	0 (0.0)
Extracardiac Stimulation - LV	35 (32)	7	7 (3.5)	28	27 (13.4)
Unable To Capture - LV	2 (2)	2	2 (1.0)	0	0 (0.0)
Subtotal LV Lead Related Events	**46 (42)**	**18**	**17 (8.4)**	**28**	**27 (13.4)**
Procedure Related Events (N at risk =210)					
Adverse Reaction - General	1 (1)	1	1 (0.5)	0	0 (0.0)
Adverse Reaction - Hypotension	2 (2)	2	2 (1.0)	0	0 (0.0)
Adverse Reaction - Respiratory	2 (2)	2	2 (1.0)	0	0 (0.0)
Coronary Venous Dissection	2 (2)	0	0 (0.0)	2	2 (1.0)
Coronary Venous Perforation Without Tamponade	1 (1)	0	0 (0.0)	1	1 (0.5)
Hematoma - Pocket (<=30 Days Post-Implant)	9 (9)	2	2 (1.0)	7	7 (3.3)
Inadvertent VT/VF	1 (1)	0	0 (0.0)	1	1 (0.5)
Myocardial Perforation With Tamponade	1 (1)	1	1 (0.5)	0	0 (0.0)
Other-Lead-Procedure	2 (2)	2	2 (1.0)	0	0 (0.0)
Other-PG system-Procedure	1 (1)	0	0 (0.0)	1	1 (0.5)
Pericardial Effusion	2 (2)	1	1 (0.5)	1	1 (0.5)
Pneumothorax - Procedure	4 (4)	3	3 (1.4)	1	1 (0.5)
Post-Surgical Infection (<= Days Post-Implant)	1 (1)	0	0 (0.0)	1	1 (0.5)
Post-Surgical Pocket Hemorrhage	1 (1)	1	1 (0.5)	0	0 (0.0)
Post-Surgical Wound Discomfort	11 (11)	2	2 (1.0)	9	9 (4.3)
Renal Failure Due To Contrast Media - Procedure	1 (1)	1	1 (0.5)	0	0 (0.0)
Venous Occlusion	1 (1)	1	1 (0.5)	0	0 (0.0)
Failure To Implant Epicardial LV Lead	1 (1)	1	1 (0.5)	0	0 (0.0)
Inability To Place The LV Lead	1 (1)	1	1 (0.5)	0	0 (0.0)
Left Chest Wall Emphysema	1 (1)	0	0 (0.0)	1	1 (0.5)
Unable To Insert LV Lead With Initial Procedure	1 (1)	1	1 (0.5)	0	0 (0.0)
Subtotal Procedure Related Events	**47 (38)**	**22**	**19 (9.0)**	**25**	**23 (11.0)**
Cardiovascular - HF Related Events (N at risk =210)					
Dyspnea - Heart Failure	16 (12)	13	9 (4.3)	3	3 (1.4)
Gastrointestinal - Heart Failure	1 (1)	1	1 (0.5)	0	0 (0.0)
Heart Failure Symptoms - Unspecified	6 (6)	5	5 (2.4)	1	1 (0.5)

		Complications		Observations	
Adverse Event	**Total Events (N Subjects)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
Hypertension - Heart Failure	1 (1)	0	0 (0.0)	1	1 (0.5)
Hypotension - Heart Failure	2 (2)	1	1 (0.5)	1	1 (0.5)
Multi-System Failure - Heart Failure	5 (5)	5	5 (2.4)	0	0 (0.0)
Multiple Heart Failure Symptoms	41 (29)	33	24 (11.4)	7	5 (2.4)
Peripheral Edema - Heart Failure	3 (3)	1	1 (0.5)	2	2 (1.0)
Pulmonary Edema - Heart Failure	2 (2)	2	2 (1.0)	0	0 (0.0)
Renal Insufficiency - Heart Failure	1 (1)	1	1 (0.5)	0	0 (0.0)
Weight Gain - Heart Failure	1 (1)	0	0 (0.0)	1	1 (0.5)
Subtotal Cardiovascular - HF Related Events	**79 (47)**	**62**	**36 (17.1)**	**16**	**14 (6.7)**
Cardiovascular - Non-HF Related Events (N at risk =210)					
Arterial/Venous Trombolytic Event	1 (1)	0	0 (0.0)	1	1 (0.5)
Atrial Fibrillation (AF)	20 (17)	8	7 (3.3)	12	11 (5.2)
Atrial Flutter	7 (5)	5	4 (1.9)	2	2 (1.0)
Atrial Tachyarrhythmias	3 (3)	0	0 (0.0)	3	3 (1.4)
Cardiac Arrest	8 (8)	8	8 (3.8)	0	0 (0.0)
Cardiogenic Shock	1 (1)	1	1 (0.5)	0	0 (0.0)
Cerebrovascular Accident (CVA)	1 (1)	0	0 (0.0)	1	1 (0.5)
Chest Pain - Ischemic	4 (4)	0	0 (0.0)	4	4 (1.9)
Chest Pain - Other	8 (8)	1	1 (0.5)	7	7 (3.3)
Coronary Artery Disease	2 (1)	1	1 (0.5)	1	1 (0.5)
Dizziness	5 (4)	1	1 (0.5)	4	3 (1.4)
Fatigue	1 (1)	0	0 (0.0)	1	1 (0.5)
Hypotension	2 (2)	2	2 (1.0)	0	0 (0.0)
Intracardiac Thrombus	1 (1)	1	1 (0.5)	0	0 (0.0)
Mitral Regurgitation	2 (2)	1	1 (0.5)	1	1 (0.5)
Multiple Symptoms	1 (1)	1	1 (0.5)	0	0 (0.0)
Myocardial Infarction	5 (5)	5	5 (2.4)	0	0 (0.0)
Nonsustained Ventricular Tachycardia (NSVT)	2 (2)	0	0 (0.0)	2	2 (1.0)
Other-Patient Condition-Cardiovascular	1 (1)	0	0 (0.0)	1	1 (0.5)
Palpitations	2 (2)	1	1 (0.5)	1	1 (0.5)
Peripheral Vascular Disease	4 (4)	4	4 (1.9)	0	0 (0.0)
Premature Ventricular Contractions (PVC)	2 (2)	0	0 (0.0)	2	2 (1.0)
Sinus Tachycardia	2 (2)	1	1 (0.5)	1	1 (0.5)
Syncope	4 (4)	1	1 (0.5)	3	3 (1.4)
Thromboembolic Events	1 (1)	0	0 (0.0)	1	1 (0.5)
Transient Ischemic Attack (TIA)	1 (1)	0	0 (0.0)	1	1 (0.5)
Ventricular Fibrillation (VF)	2 (2)	1	1 (0.5)	1	1 (0.5)
Ventricular Flutter	1 (1)	0	0 (0.0)	1	1 (0.5)

		Complications		Observations	
Adverse Event	**Total Events (N Subjects)**	**Events**	**Subjects (%)**	**Events**	**Subjects (%)**
Ventricular Tachyarrhythmias	1 (1)	0	0 (0.0)	1	1 (0.5)
Ventricular Tachycardia (VT)	7 (6)	2	2 (1.0)	5	4 (1.9)
Subtotal Cardiovascular - Non-HF Related Events	**102 (66)**	**45**	**35 (16.7)**	**57**	**43 (20.5)**
Subtotal Non-cardiovascular Related Events	**226 (88)**	**120**	**52 (24.8)**	**101**	**59 (28.1)**
Ablation Related Events (N at risk =202)					
Pleural Effusion	2 (1)	2	1 (0.5)	0	0 (0.0)
Pulmonary Edema	1 (1)	1	1 (0.5)	0	0 (0.0)
Subtotal Ablation Related Events	**3 (2)**	**3**	**2 (1.0)**	**0**	**0 (0.0)**
Events Pending Final Classification					
Pending	10 (9)	2	2 (1.0)	3	3 (1.5)
Subtotal Events Pending Final Classification	**10 (9)**	**2**	**2 (1.0)**	**3**	**3 (1.5)**

4.5. Death Summary

Seventeen (17) deaths have been reported in the CAPTIVATE study as of the date of the final data pull for this report (7.9% of enrolled subjects). Twelve (12) deaths have been adjudicated by the CEC, the remaining 5 deaths are pending complete adjudications (referred to as “pending classification” in the table below).

Table 4.5-1: Death Summary

	Number (%) of Subjects					
	Classification Source		Related to AUTOGEN PG (CEC Classification)			
Primary Organ Cause	**Site**	**CEC**	**Yes**	**No**	**Unknown**	**Not Classified**
Cardiac: Arrhythmic	3 (1.4%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Cardiac: Ischemic	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Cardiac: Other Cardiac	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac: Pump Failure	7 (3.2%)	5 (2.3%)	0 (0.0%)	5 (2.3%)	0 (0.0%)	0 (0.0%)
Cardiac: Unknown	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non Cardiac	1 (0.5%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Pending	3 (1.4%)	5 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.3%)
Unknown	1 (0.5%)	4 (1.9%)	0 (0.0%)	3 (1.4%)	1 (0.5%)	0 (0.0%)
Total	**17 (7.9%)**	**17 (7.9%)**	**0 (0.0%)**	**11 (5.1%)**	**1 (0.5%)**	**5 (2.3%)**

5. Conclusions

The results from this clinical study establish the safety and effectiveness of the AUTOGEN family of devices with the PaceSafe Right Ventricular Autothreshold (RVAT) and Left Ventricular Autothreshold (LVAT) features. The Safety Endpoint analyzed system-related complication-free rate at 3-months post-implant follow up period which demonstrated safety for the AUTOGEN system. Effective performance of the RVAT and LVAT features was exhibited by evaluation of RVAT and LVAT commanded and ambulatory accuracy at 1-month and 3-month follow-up visits. The results of the CAPTIVATE study are applicable for the AUTOGEN CRT-D and ICD devices. In conclusion, this clinical study demonstrated the safety and effectiveness of AUTOGEN with RVAT and LVAT features when used in accordance with its labeling.

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