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CLINICAL SUMMARY

IVORY STUDY

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CLINICAL STUDY - SUMMARY OF IVORY STUDY

The IVORY study was designed to evaluate the safety and effectiveness of the Right Atrial Automatic Threshold (RAAT) feature and the effectiveness of the RYTHMIQ™ feature.

STUDY DESIGN

IVORY was a prospective, multi-center study designed to gather data on dual-chamber pacemaker and cardiac resynchronization therapy pacemaker (CRT-P) indicated patients. Boston Scientific leads were recommended but were not required.

RYTHMIQ was evaluated as a randomized within-patient, single-blinded secondary endpoint in pacemaker patients. RAAT endpoints were evaluated in a single-arm, non-randomized fashion.

METHODS

The study enrolled patients receiving VITALIO™ pacemakers or INTUA™ cardiac resynchronization therapy pacemakers, both from the Ingenio family of devices. Both VITALIO and INTUA devices included the RAAT feature. VITALIO pacemakers included the RYTHMIQ feature.

All patients with implanted devices were required to be followed at implant, pre-discharge, one month, and three months for endpoint analyses.

RAAT effectiveness was evaluated at the one-month and three-month visits by the following endpoints:

- The accuracy of Commanded RAAT was evaluated by determining the equivalence of the manual unipolar and commanded automatic threshold test results (0.5 V equivalence margin). The percent of equivalent tests was compared to a performance goal of 90%.
- The accuracy of Ambulatory RAAT was evaluated by determining the equivalence of the results from the Ambulatory Threshold Test and the commanded automatic threshold test performed in-office (1.0 V equivalence margin). The most recent Ambulatory RAAT that occurred within the seven days prior to the one-month and three-month follow-up visits was compared to the commanded automatic threshold measured at the corresponding follow-up visit.

The percent of equivalent paired threshold tests was compared to a performance goal of 90%.

- The percent of Commanded RAAT tests that resulted in an appropriate outcome was evaluated. An appropriate outcome was defined as a test that resulted in a commanded threshold or a test that resulted in an appropriate RAAT code. An appropriate code was defined in the protocol as a condition beyond the control of the RAAT algorithm, such as atrial fibrillation.

RYTHMIQ effectiveness was assessed by the relative reduction of RV pacing percent at the three-month visit. A crossover design was employed, in which patients served as their own control and were randomized to the order of RYTHMIQ programming (ON then OFF or OFF then ON).

The safety of the investigational pulse generators used in this study was evaluated by the system-related complication-free rate at 90 days post-implant. A system-related complication was defined as an adverse event resulting in death, serious injury, correction using invasive intervention, or permanent loss of device functions related to the implanted system, except for those related to the left ventricular lead for patients receiving a CRT-P device.

The secondary safety endpoint was designed to demonstrate that the RAAT feature produced a sufficient pacing output voltage able to capture the right atrium. The proportion of tests with RAAT output greater than or equal to the maximum of the manual unipolar and bipolar thresholds plus a 0.5 V delta as a safety margin was compared to a performance goal of 90%.

RESULTS

Patient Demographics

Fifteen centers enrolled 139 patients of which 132 were implanted with a study device. The first enrollment occurred on 11 October 2011 and the final three-month visit occurred on 21 June 2012.

The mean age of VITALIO patients was 73 years, and 60% were male. The mean age of INTUA patients was 73 years, and 65% were male.

RAAT Effectiveness Endpoints

Table 1 shows the summary statistics for the RAAT effectiveness endpoints.

Table 1. Accuracy of the Commanded RAAT Feature

Assessment	Expected Value	Performance Goal	Result (Lower Confidence Limit)	p-value
Percent of Commanded RAAT Tests that Result in an Accurate Threshold	97.5%	90%	100% (98.4%)	<.001
Percent of Ambulatory RAAT Tests that Result in an Accurate Threshold	99%	90%	99.5% (97.5%)	<.001
Percent of Commanded RAAT Tests that Result in an Appropriate Outcome	87.5%	70%	84.7% (80.4%)	<.001

All Commanded RAAT tests resulted in an accurate threshold when compared to the manual threshold test. The Ambulatory RAAT output met equivalency for 99.5% of subsequent commanded automatic tests. Commanded tests resulted in an appropriate outcome in 84.7% of tests, 81.0% of which produced a threshold.

The RAAT feature is based on capturing the evoked response signal between two electrodes. The RAAT feature was consistently observed to measure a sufficient evoked response in the majority of lead families and the pacing amplitude was set with an appropriate safety margin above the stimulation threshold. It was observed that the evoked response amplitude detected from one lead family¹ in the study with small electrode spacing (~1 mm) was less likely to be sufficient to ensure threshold detection; in these instances the pacing amplitude defaulted to 5.0 V.

There was no difference in RAAT endpoints by CRT-P or Pacemaker devices.

RYTHMIQ Effectiveness Endpoint

Chronic success for this endpoint was assessed by a median relative reduction of right ventricular pacing percent for RYTHMIQ programmed to ON vs. RYTHMIQ programmed to OFF. All patients received both RYTHMIQ programmed to ON and programmed to OFF in two consecutive periods, where the patient's programming allocation was randomized for the first period. Then a crossover to the alternate setting occurred for the second period once the end of the first period was reached.

1. STJ 1999 Lead Family

Patients with permanent third-degree AV block were not included in the statistical analysis of this endpoint but were randomized following the same methodology to show that no additional adverse events related to RYTHMIQ were observed.

The median of the within-patient relative reductions in RV pacing comparing RYTHMIQ ON to OFF is shown in Table 2.

Table 2. Relative Reduction in RV Pacing With RYTHMIQ On

Assessment	Expected Value	Performance Goal	Observed Median (25th, 75th percentiles)	p-value
Relative Reduction in RV Pacing Percent	2%	0%	80% (6%, 99%)	<.001

The median RV pacing percentage with RYTHMIQ ON was 4% compared to 98% with RYTHMIQ OFF. The median of the within-patient relative reductions in RV pacing percentage was 80%.

Implanted or attempted patients with permanent third-degree AV block (N=15) were not included in the statistical analysis of this endpoint but followed according to the same programming scheme as the other IVORY patients. Patients with permanent third-degree AV block did not experience a reduction in RV pacing with RYTHMIQ ON compared to OFF, indicating maintenance of appropriate pacing in a chronic setting. There were no adverse events in patients with permanent third-degree AV block that were related to RYTHMIQ.

Safety Endpoints

Safety endpoints for the IVORY study are shown in Table 3.

Table 3. Safety Endpoints

Assessment	Expected Value	Performance Goal	Result % (Lower Confidence Limit)	p-value
System-Related Complication-Free Rate	90%	80%	87.5% (81.8%)	0.002
Percent of Tests That Result in a Sufficient Output	98%	90%	100% (98.5%)	<.001

The study passed the primary safety endpoint by internal committee classification of adverse events. All patients achieved a sufficient pacing output voltage via

Commanded RAAT at the one-month and the three-month follow-up visits. There was no difference in the primary safety endpoint by device type.

CONCLUSION

The IVORY data show:

- The Commanded RAAT Threshold Test produced an accurate threshold in 100% of cases.
- The Ambulatory Threshold Test produced by the RAAT feature is accurate in comparison to the in-office threshold test.
- The percent of Commanded RAAT tests that resulted in appropriate RAAT performance met the expected performance goal.
- The RYTHMIQ feature effectively reduces RV pacing.
- The Ingenio pacemaker and CRT-P systems are safe as assessed by the system-related complication-free rate. The system-related complication-free rate for IVORY met the performance goal, indicating that the overall safety profile of the implanted system is similar to approved devices.
- RAAT safely establishes a sufficient pacing output.

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