Statistical Analysis Plan

Version AA

NAVIGATE X4

C1481

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Revision History

Version AA - Initial Release

Original Release: February 25, 2015

Revision History

Revision Number/Release Date	Section	Change	Reason for Change
Version AA/ 25FEB2015	All	N/A	Initial Release

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1 PLANNED PROTOCOL ANALYSES

All information necessary to complete the required analyses for the NAVIGATE X4 study are contained within the NAVIGATE protocol. Additional information is found in the following section2.

2 ADDITIONAL INFORMATION

2.1 Definition of ACUITY X4 dataset

The protocol states that data from the first 748 subjects will be used to support ACUITY X4 approval. This assumes that X4 Cohort 1 (534 spiral leads) and X4 Cohort 2 (214 straight leads) finish enrolling at the same time. However, the X4 Cohort 2 finished enrolling first. Therefore, the ACUITY X4 dataset will be defined as all subjects enrolled on or before the date of the 534th X4 Cohort 1 enrollment.

2.2 Definition of RELIANCE 4-FRONT dataset

The total number of leads included in the dataset used to support FDA approval will equal 1876. The majority of leads will be taken from the NAVIGATE X4 study; the remaining leads will be taken from separate studies studying the 4-FRONT lead.

2.3 Index Procedure

As stated in the protocol, the final lead implanted or attempted in a chamber from the initial procedure will contribute to the analysis of all applicable endpoints. This criterion will apply separately for ACUITY X4 and RELIANCE 4-FRONT.

2.4 Planned Futility Analysis

As stated in the protocol, a futility analysis for each investigational lead – ACUITY X4 and RELIANCE 4-FRONT – will be conducted for each primary effectiveness endpoint.

2.4.1 Timing

For ACUITY X4 the futility analysis will occur no sooner than the point at which 374 subjects have been enrolled for 3 months. For RELIANCE 4-FRONT the futility analysis will occur at the same time as that for ACUITY X4 or when 50 subjects with a RELIANCE 4-FRONT have been enrolled for 3 months, whichever is later.

2.4.2 Execution

The futility analysis will be performed by a BSC statistician independent from the NAVIGATE X4 study team. The independent statistician will communicate to the study team only whether or not the conditional power is found to be less than 20%, and that information will be communicated to FDA as well. BSC may consider terminating enrollment if the conditional power is found to be less than 20%.

2.4.3 Futility Analysis Details

Conditional power will be calculated using a mixture of observed patient endpoint data and expected results from patients without endpoint data yet collected. Expected results will be based on the sample size assumptions stated in the protocol. Each patient without data will have their specific endpoint result randomly generated from a distribution based from the sample size assumptions stated in the protocol. The endpoint results will be calculated across 10,000 simulated studies. The percent of endpoint analyses that reject the null hypothesis will be considered successful. If the percent of successful endpoint analyses is less than 20%, then the endpoint will be deemed futile. Three endpoints will be assessed separately using this methodology:

- ACUITY X4 Primary Effectiveness Endpoint 1
- ACUITY X4 Primary Effectiveness Endpoint 2
- RELIANCE 4-FRONT Primary Effectiveness Endpoint

2.5 Endpoint Analysis Timing

For either lead – ACUITY X4 or RELIANCE 4-FRONT – the endpoint analyses can occur for primary cohort (cohort 1) prior to performing analyses for the secondary cohort (cohort 2). However, analyses for cohort 2 cannot be performed prior to the analyses for cohort 1.