STATISTICAL ANALYSIS PLAN: OBSERVE-IVA

A Randomized, Double-Blind, Placebo-Controlled Trial Assessing the Efficacy of Ivabradine Initiated at the Time of Discharge from the Observation Unit

NCT: 03168529

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Phillip Levy
plevy@wayne.edu

Statistical Analysis Plan:

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(OBSERVE-IVA)

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The original plan detailed in the protocol is as follows:

13.0 Statistical Analysis The primary outcome (change in heart rate i.e. the value at Day 28 (+/-2) - the value at baseline) will be analyzed as two sample t-test. Secondary outcomes that are continuous variables will be analyzed as two sample t-test. The safety endpoint of unplanned visits will be compared as the number of unplanned medical visits over the study period tested using Poisson regression.

14.0 Sample Size And Power Based on the SHIFT1 study, the mean heart rate reduction with IVA is 8 bpm with a standard deviation of 13 bpm. A sample size of 57 in each group will have 90% power to detect a difference in means of 8.0 assuming that the common standard deviation is 13.0 using a two group t-test with a 0.05 two-sided significance level. To account for a projected dropout rate of 15%, 66 subjects will be enrolled in each group (132 total for the study over a 2-year period). Furthermore, we expect that our centers will recruit a cohort that is 75% self-identified African Americans. This number (n=99) will provide 80% power to detect the same effect size when analyzed in African Americans only.

Unfortunately, formal statistical analysis was not completed due to low sample size. Unfortunately, OBSERVE IVA fell far short of its enrollment goal with just 19 out of a targeted 132 subjects included in the final study cohort. Because of this, we have not developed any abstracts, manuscripts or other publications to date, though we may do so in the future. Of the 19 enrollments, 6 were at Detroit Receiving Hospital, 8 at Sinai-Grace Hospital, 2 at Harper University Hospital, and 3 at Henry Ford Hospital. A total of 13 subjects (68%) received ivabradine (IVA) and 6 received matching placebo. Baseline data for the overall study cohort and by randomization are provided in the accompanying **Table** with corresponding notation regarding the approach to statistical analysis. While no formal comparison has been performed, data showing heart rate at each of the 3 study visits for the 19 subjects enrolled and by study group are provided in the accompanying **Figure**.

Table: Baseline data for OBSERVE IVA study cohort

Baseline Statistical Summary for OBSERVE-IVA											
		All			IVA			Placebo			
Measure	Response	N or N(%)	Mean (SD)	Median (Q1,Q3)	N or N(%)	Mean (SD)	Median (Q1,Q3)	N or N(%)	Mean (SD)	Median (Q1,Q3)	p-Value
Demographics											
Age		19	61.7 (12.1)	60 (53, 72)	13	62.7 (13.4)	60 (53, 72)	6	59.7 (9.6)	59 (54, 65)	0.5839[b]
Sex	Male	14 (73.7)			8 (61.5)			6 (100)			0.1280[e]
Race	African American	18 (94.7)			12 (92.3)			6 (100)			
Ethnicity	Not Hispanic or Latino	19 (100)			13 (100)			6 (100)			N/A
BMI		19	34.3 (9.3)	33.3 (26.6, 39.3)	13	35.5 (10.2)	35.7 (29.1, 39.3)	6	31.5 (6.9)	32.1 (26.6, 35.8)	0.3282[b]
Past Medical History											
Heart Failure	Yes	19 (100)			13 (100)			6 (100)			N/A
HTN	Yes	18 (94.7)			13 (100)			5 (83.3)			0.3158[e]
Stroke	Yes	3 (15.8)			2 (15.4)			1 (16.7)			1.0000[e]
MI	Yes	8 (42.1)			5 (38.5)			3 (50)			1.0000[e]
Revascularization	Yes	7 (36.8)			4 (30.8)			3 (50)			0.6169[e]
PVD	Yes	6 (31.6)			4 (30.8)			2 (33.3)			1.0000[e]
Chronic Renal Insufficiency	Yes	5 (26.3)			4 (30.8)			1 (16.7)			1.0000[e]
Arrythmia	Yes	4 (21.1)			3 (23.1)			1 (16.7)			1.0000[e]
EF (%)		18	25.7 (6.13)	25 (20, 30)	12	25.7 (6.87)	25 (20, 32.5)	6	25.8 (4.92)	25 (25, 25)	0.9225[c]
Vital Signs											
SBP (mmHg)		19	122 (15)	118 (112, 137)	13	123 (16)	118 (112, 137)	6	120 (13)	120 (115, 129)	0.7298[b]
DBP (mmHg)		19	77 (9)	78 (69, 80)	13	76 (9)	78 (69, 80)	6	78 (10)	76 (74, 86)	0.6040[b]
Heart Rate (bpm)		19		88 (81, 97)	13		88 (81, 97)	6		85 (81, 91)	0.9309[c]
Lab Results											
Na (mmol/L)		19	139 (2)	140 (138, 141)	13	139 (3)	141 (138, 141)	6	138 (2)	138.5 (137, 140)	0.1403[b]
Troponin (ng/dL)		10	0.05 (0.03)	0.04 (0.04, 0.05)	7	0.06 (0.04)	0.04 (0.04, 0.05)	3	0.04 (0.00)	0.04 (0.04, 0.05)	0.8001[c]
GFR		18	76 (22	78 (57, 94)	12	73 (23)	72 (54, 92)	6	83 (16)	84 (74, 98)	0.3136[b]

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[a] - t-Test using Pooled Variance
[b] - t-Test using Satterthwaite Combined Variance
[c] - Wilcoxon Rank Sum - t-Test Approximation
[d] - Chi-Squared Test
[e] - Fisher's Exact Test

Figure: Heart rate trends by study visit (1= baseline, 2 = 15 days, 3 = 30 days)