

Draft Questions for the Chronicle Advisory Panel Meeting

Effectiveness

1. Results of the effectiveness endpoints of the COMPASS-HF study (a randomized clinical trial that enrolled both NYHA class III and IV patients) compared the Chronicle arm (where physicians had access to the Chronicle data) to the control arm (where physicians did not have access to the Chronicle data). The pre-specified, alpha-allocated primary effectiveness endpoint was a comparison between the two arms of the rate of heart failure related hospital equivalents through 6 months.

The hypothesis was stated as follows:

“The CHRONICLE group will have a significantly lower rate of heart failure related hospital equivalents than the CONTROL group through 6 months.”

The pre-specified, alpha-allocated primary effectiveness analysis identified an event rate of 0.67 and 0.85 for the Chronicle and Control patients, respectively – an absolute reduction of 0.18 hospital equivalents per patient per 6 months. This 21% reduction in overall HF-related hospital equivalents was not statistically significant (with a p-value of 0.33 using the Negative Binomial Regression technique). The null hypothesis was not rejected.

Please provide your clinical and/or statistical interpretation of the results of the primary effectiveness endpoint analysis in the entire study population.

2. The sponsor’s pre-specified sub-group analysis illustrated that the impact of Chronicle Guided Care was consistent across several sub-groups, except NYHA class. Despite the fact that the interaction p-value for NYHA Class was not significant ($p=0.08$), there was a directional difference in the response to Chronicle Guided Care between NYHA Class III and IV patients. As a result, additional analyses were conducted to examine the differential effect with respect to NYHA class. Please note that alpha was not prospectively assigned for these analyses.
 - a. For the NYHA class III subjects, overall event rates were 0.54 and 0.85 in the Chronicle and Control patients, respectively – an absolute reduction of 0.31 hospital equivalents per patient per 6 months. This 36% reduction resulted in a p-value of 0.058 using the Negative Binomial Regression technique.

Please provide your clinical and/or statistical interpretation of the results of the primary effectiveness endpoint analysis in the NYHA class III patient population alone.

- b. For the NYHA class IV subjects, overall event rates were 1.44 and 0.89 in the Chronicle and Control patients, respectively – an absolute *increase* of 0.55

hospitalization equivalents. This 62% increase resulted in a p-value of 0.27 using the Negative Binomial Regression technique.

Please provide your clinical and/or statistical interpretation of the results of the primary effectiveness endpoint analysis in the NYHA class IV patient population alone.

3. The sponsor performed *post hoc* analyses to assess whether the NYHA Class IV subjects randomized to the Chronicle arm were actually sicker than the NYHA Class IV subjects randomized to the Control arm. Based on these findings, the sponsor examined several other baseline patient characteristics to determine which covariates possibly had added influence on the primary endpoint outcome. These *post hoc* analyses illustrated that there were small, yet potentially important, imbalances between the two study groups (Chronicle and Control) with respect to several baseline clinical characteristics associated with the primary outcome measure in the study. The sponsor hypothesized that controlling for these baseline clinical characteristics in all study patients may reveal the true effect of Chronicle Guided Care. To adjust for the influence of these predictive characteristics on the primary endpoint of the study, the sponsor implemented a multivariable adjustment methodology.

Please provide your clinical and/or statistical interpretation of the results of the *post hoc* effectiveness analyses using the multivariable adjustment methodology.

4. The sponsor collected data on several secondary endpoints in the COMPASS-HF study. These included the following:
 - Health care utilization
 - Days alive out of the hospital
 - Patient survival
 - Rate of adverse events
 - Predictive value of pressure change in the CONTROL group
 - Composite response endpoint
 - Quality of life
 - New York Heart Association (NYHA) Functional Class
 - Distance walked in six minutes

While there were no pre-specified performance criteria or statistical hypotheses for these endpoints, they do represent a spectrum of meaningful measures for the heart failure population. The results for these endpoints were presented for the entire patient population and also analyzed by NYHA Class.

Please provide your clinical and/or statistical interpretation of the secondary endpoint results for the COMPASS-HF study.

Safety

5. Results of the safety endpoints of the COMPASS-HF clinical trial compared specific adverse events in the subjects implanted with the device to objective performance criteria (OPC) determined from the pacemaker medical literature. The primary safety endpoints were:
 - Freedom from system-related complications at 6 months; and
 - Freedom from pressure sensor failure at 6 months.

The OPC established for the freedom from system-related complications at 6 months was 80%. The freedom from system-related complications rate through 6 months was 91.5% with a lower one-sided 95.10% confidence bound of 88.7%, which is above the predetermined performance criterion of 80%.

The OPC established for the freedom from pressure sensor failure at 6 months was 90%. The freedom from pressure sensor failure rate through 6 months was 100% with a lower one-sided 95.10% confidence interval of 98.9%, which is above the predetermined objective of 90%.

Please provide your clinical and/or statistical interpretation of the results of the primary safety endpoint analysis.

6. In addition to the other secondary endpoints (discussed above) in the COMPASS-HF trial, the sponsor collected data on patient survival. While the number of deaths during the 6 month randomized follow-up period was similar in both arms (13 deaths in the Chronicle arm vs. 11 deaths in the Control arm), the survival curves separate after the first 6 months. In particular, the survival curves separate for the NYHA class IV subgroup after the randomized period.

Please provide your clinical and/or statistical interpretation of the survival analyses discussed in the panel pack and presentations.