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HFN-LIFE Statistical Analysis Plan 2020-09-11

Statistical Analysis Plan

Entresto™ (LCZ696) In Advanced Heart Failure

LIFE

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January 24, 2017

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June 15, 2017

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February 20, 2019

Sponsor
National Heart, Lung and Blood Institute

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1. Overview

1.1 Synopsis

The *Entresto™ (LCZ696) In Advanced Heart Failure (LIFE)* study is a randomized, double-dummy, active-comparator trial to assess the effect of LCZ696 (sacubitril and valsartan) versus Valsartan, with dose up-titration, on the proportional change from baseline in the AUC for NT Pro BNP levels. The eligible patient population consists of those with symptomatic, advanced heart failure due to left ventricular systolic dysfunction. Randomized study treatment will take place for a total of 24 weeks.

1.2 Study Treatments

Each patient will be randomized to receive either LCZ696 (sacubitril and valsartan) + valsartan-placebo or Valsartan + LCZ696-placebo. Study treatment will be titrated to the target dose of 200 mg LCZ696 as two 100 mg LCZ696 and 2 placebo tablets po BID or to the target dose of 160 mg Valsartan as two 80 mg Valsartan and 2 placebo tablets po BID. Randomized subjects will receive the first dose of study drug as follows:

- For subjects not previously taking an ACE Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB), previously taking an ACEI or ARB at a low dose, or subjects who have an eGFR < 30 mL/min/1.73m², the starting dose of valsartan will be 40 mg po BID and the starting dose of LCZ696 will be 50 mg po BID.
- For subjects taking an ACEI or ARB at greater than low dose, the starting dose of valsartan will be 80 mg po BID and the starting dose of LCZ696 will be 100 mg po BID.

Dose adjustments will be performed every 2 weeks by doubling the dose of LCZ696 or valsartan up to the target maximum dose. The doses of LCZ696 are 50 mg (one 50 mg active and one placebo tablet), 100 mg (one 100 mg active and one placebo tablet) and 200 mg (two 100 mg active and two placebo tablets). The doses of valsartan are 40 mg (one 40 mg active and one placebo tablet), 80 mg (one 80 mg active and one placebo tablet), and 160 mg (two 80 mg active and two placebo tablets).

2. Study Design

2.1 Overview

The LIFE study is a randomized, double-dummy, active-comparator study in heart failure patients with reduced ejection fraction. A planned total of approximately 400 patients will be randomized in the study.

The randomized treatments in this study are blinded. Treatment is expected to last for 24 weeks.

The over-arching hypothesis is that, compared to Valsartan alone, treatment with LCZ696 will lead to improvements in NT Pro BNP levels, which reflect hemodynamic and clinical status.

2.2 Randomization

Patients are randomized in a 1:1 ratio to either LCZ696 + Valsartan-placebo or Valsartan + LCZ696-placebo. The randomization scheme consists of a permuted block design with stratification by clinical site and atrial fibrillation status.

2.3 Data Sources

A database of case report form and biomarker core lab data will be created in Inform, and the data then transferred to SAS for analysis. The randomized treatment assignment will be provided through data provided by the Webez system, an Almac Clinical Services web-based randomization system. The data is stored on Solaris server uxctstp01 in the folder /dcri/ct/hf_net/LIFE/data.

3. Analysis Population and Missing Data

All randomized patients will be included in the analysis population for assessing the primary, secondary, tertiary, and exploratory endpoints. All endpoints will be analyzed on an intent-to-treat basis.*

However, as described in subsequent sections of this document, some patients may be excluded from certain analyses if key data elements are missing. With the extensive efforts being made in collaboration with the clinical sites to ensure data quality and completeness, it is expected that exclusion of patients for any endpoint analysis will be minimal. The specific endpoint descriptions in Sections 9 through 12 describe the circumstances that would lead to a patient being excluded from a specific analysis.

*** Analysis Modifications to Address COVID-19 Pandemic**

The coronavirus COVID-19 pandemic has had a major impact on the performance of the LIFE trial. It was anticipated that patients will have greater difficulty attending study visits on their planned schedule due to restrictions on outpatient visits at many institutions. Therefore, patients will be unable to participate in study-related procedures such as biomarker sample collection, which comprises the primary endpoint for this trial. Additionally, due to restrictions on clinic access and potential concerns with patients going to the emergency department where exposure risk to COVID-19 is increased, we expect reporting of clinical endpoints such as emergency department visits and even hospital admissions to be impacted by the pandemic.

Therefore, due to the unexpected disruption brought on by the COVID-19 pandemic, the analysis plan was amended to restrict the reported program analyses to those patients that had their Week 12 visit prior to March 1, 2020, when the COVID-19 pandemic became more active in the continental United States. This translated to restricting the reported analyses to patients that were randomized on December 7, 2019 or earlier. Additionally, any study data collected after March 1, 2020 were excluded from the analyses for those patients randomized on or prior to December 7, 2019. This amended population will be labeled as the pre-COVID-19 population within the analysis plan.

The original protocol-specified analyses were to be conducted on all randomized patients using all available information. Those analyses will still be performed but will be considered to be sensitivity analyses.

Of the 365 patients randomized, 335 will be included in the pre-COVID-19 population. Twenty five of the 335 patients will have some visit information removed due to study visits occurring March 1, 2020 or later. The

remaining 30 patients will only contribute to the original protocol-specified analyses, now part of the sensitivity analyses.

4. General Methodology

Medians, 25th and 75th percentiles will be presented for continuous variables; the number and percentage of patients in each category will be presented for categorical variables. For all endpoints a p-value ≤0.05 will be considered statistically significant and all tests will be 2-sided. Analyses will be performed using validated SAS software (SAS Institute, Inc., Cary, NC). Appropriate statistical models will be used to examine the effect of treatment on both the primary, secondary, and tertiary outcomes in the study.

The modeling that will be used for each endpoint will be detailed within each endpoint description section.

5. Primary Endpoint

Primary Endpoint
#1: The proportional change from baseline in the area under the curve (AUC) for NT Pro BNP levels measured at baseline, weeks 2, 4, 8, 12 and 24.

See Section 9 for a detailed description of the primary endpoint, including rules used for handling incomplete data.

6. Secondary Endpoints

Secondary Endpoints (Efficacy)
#1: Days alive and out of hospital at 24 weeks, not listed for transplant (Status 1A, 1B or 1-4) or undergoing transplant, implanted with an LVAD, maintained or started on continuous inotropic therapy for ≥ 7 days, or has had two hospital admissions for heart failure (HF), other than the index admission. The days alive and out of hospital will end on the day of the second HF readmission, if applicable.

Secondary Endpoints (Tolerability)
#2: Tolerability measured as number of subjects achieving a target dose of 25%, 50% or 100% of valsartan or LCZ696.
#3: Tolerability measured as number of subjects developing hypotension (SBP ≤ 85 mmHg) with symptoms.
#4: Tolerability measured as number of subjects developing worsening renal function (eGFR <20 ml/min/1.73m²).
#5: Tolerability measured as number of subjects developing moderate (> 5.5 mmol/L) or severe (≥ 6 mmol/L) hyperkalemia.

See Section 10 for a detailed description of each secondary endpoint, including rules used for handling incomplete data.

7. Tertiary Endpoints

Tertiary Endpoints
#1: Time to death through 24 weeks.

#2: Time to cardiovascular death through 24 weeks.
#3: Time to first heart failure hospitalization through 24 weeks.
#4: Time to death or first heart failure hospitalization through 24 weeks.
#5: Time to cardiovascular death or first heart failure hospitalization through 24 weeks.
#6: Total number of HF hospitalization admissions through 24 weeks.
#7: Number of subjects on continuous inotropic therapy ≥ 7 days after discharge from the index hospitalization through 24 weeks.
#8: Number of subjects listed for transplant (1A, 1B or 1-4), transplanted or implanted with an LVAD through 24 weeks.
#9: Change in eGFR levels compared to baseline. Renal function was assessed at baseline, weeks 2, 4, 8, 12, and 24.
#10: Change in cystatin C levels compared to baseline. Renal function was assessed at baseline, weeks 2, 4, 8, 12, and 24.
#11: Number of subjects with unanticipated use of IV diuretics (outpatient, ER or inpatient) through 24 weeks.
#12: Change in AUC in the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 4, 12, and 24 weeks compared to baseline.
#13: The change in the AUC for the ratio of NT Pro BNP/BNP from baseline to weeks 2, 4, 8, 12, and 24.
[Note: Tertiary Endpoint #13 will only be assessed on the first 200 patients randomized, as generated for the Interim Analysis. A decision was made by the Executive Committee to not assay for BNP at trial completion for the remaining randomized patients]

See Section 11 for a detailed description of each tertiary endpoint, including rules used for handling incomplete data.

8. Exploratory Endpoints

Exploratory Endpoint
#1: A four level modified clinical composite endpoint including 1) death, 2) LVAD or Heart Transplant (including listing status of 1A, 1B or 1-4), 3) multiple HF hospital admissions, and 4) single HF admission.

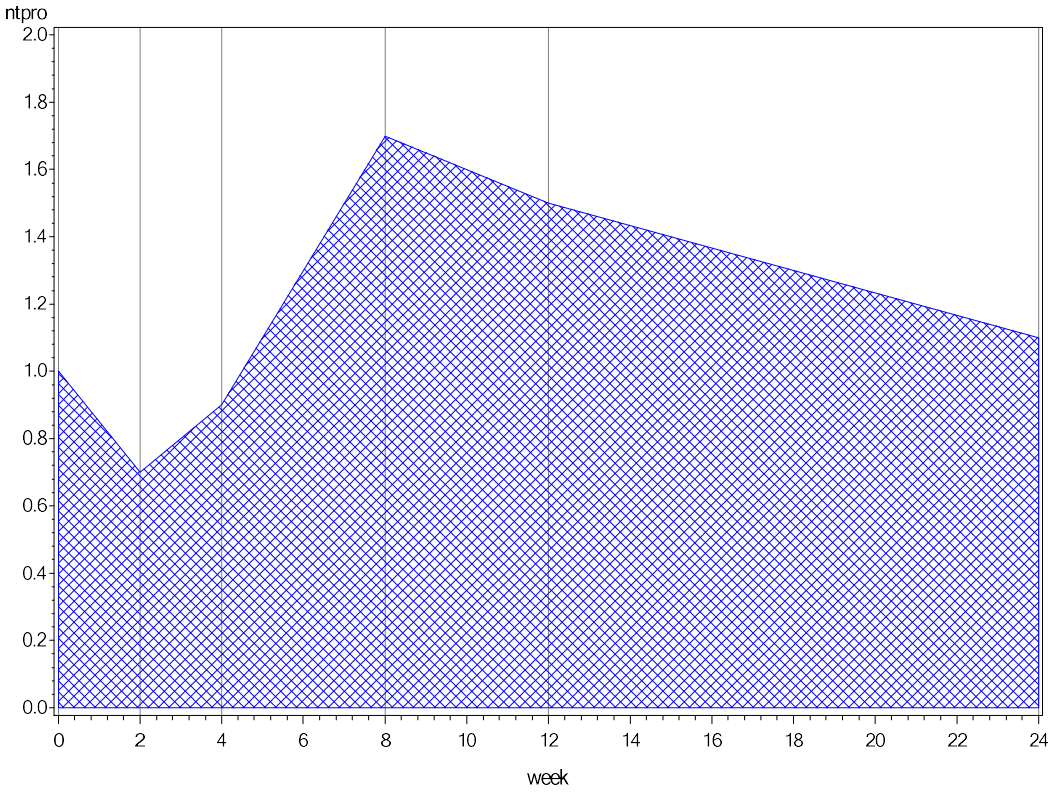
See Section 12 for a detailed description of each tertiary endpoint, including rules used for handling incomplete data.

9. Endpoint Descriptions

9.1 – Primary Endpoint

Endpoint Description: The log of the proportional change from baseline in the area under the curve for the ratio of NT Pro BNP compared to baseline, using the pre-COVID-19 population.

Response Variable Definition: All available time points will be used in the calculations. NT Pro BNP is measured at Baseline, Week 2, Week 4, Week 8, Week 12 and Week 24. The ratio of each of the post-Baseline measures will be calculated versus Baseline. The area under the entire piecewise dataset is the response variable. A visual example is provided showing a patients' hypothetical data for NT Pro BNP ratio to Baseline.



This area is determined by calculating the sum of the areas of each of the individual trapezoids. Each trapezoidal area is composed of the area bordered by the time interval on the x-axis (e.g., 0 to 2 Weeks), the respective NT Pro BNP ratio at each of the time points on the y-axis (e.g., 1 at x=0 and 0.7 at x=2), and the line segment connecting the NT Pro BNP ratios between the two y-axis values (1 and 0.7). The number of trapezoids available will depend on the completeness of the data.

It is expected that NT Pro BNP measurements may not be measured exactly at the specified time points. For example, the measurement corresponding to the 12 Week time point may actually be measured for example at 11 or 12.5 Weeks after randomization. In calculating the AUC, the measurement corresponding to Baseline will always be set at the 0 time point. Each post-Baseline visit will use the value for the visit timing, even if that timing is not exact (e.g., Week 12 visit will always assign a 12 for the x-axis). The final step in the calculation is to take log of the calculated area under the curve.

Additional Covariates in Addition to Randomized Treatment: Baseline log NT Pro BNP, atrial fibrillation status, random effect of patient

Handling of Dropouts and Missing Data: If missing NT Pro BNP at Week 24, use last observation carried forward (LOCF) from previous post-Baseline time point with available NT Pro BNP data. No adjustment will be made for missing Baseline results.

Sensitivity Analysis: Several sensitivity analyses will be performed.

1) Complete cases, using patients with available Baseline and Week 24 Week 24 NT Pro BNP data
2) For patients missing Week 24 value, impute 2.5xBaseline value for Week 24

[Note: The sensitivity analysis using imputation of 2.5xBaseline value will not be performed due to the concern that the impact of missing data due to the COVID-19 pandemic might overstate the effect of the imputation.]

3) For patients missing Week 24 value, impute 5xBaseline value for Week 24
   [Note: This sensitivity analysis using imputation of 5xBaseline value will not be performed due to the concern that the impact of missing data due to the COVID-19 pandemic might overstate the effect of the imputation.]
4) For patients that receive a left ventricular assist device (LVAD) or heart transplant prior to the Week 24 assessment, remove all NT Pro BNP results post-procedure due to the potential for an artificial response due to the procedural impacts on the heart. Missing values will be imputed in the same fashion as in the primary analysis.
5) To address a potential question seen in some journal reviews, the primary model will be run again, adding a new covariate for the effect of enrolling site.
6) Wilcoxon with worst rank imputation based on time to death and then ranking worst to best NT Pro BNP AUC for those patients that did not die prior to 24 week visit
7) Re-calculate the primary endpoint analysis and the remaining sensitivity analyses using the original ITT population.

Statistical Tests: For the Primary and Sensitivity Analyses 1 – 5, a mixed model (PROC MIXED in SAS) will be used to test the significance of differences in the area under the curve for the Log(NT Pro BNP AUC) between the two treatment arms.

For Sensitivity Analysis 6, a Wilcoxon test (PROC NPAR1WAY in SAS) will be used to test whether there is a difference in the distribution of ranks between the two treatment arms.

Interpretation of Results: A lower value for the AUC indicates an improvement in the LCX696 arm versus the Valsartan arm. Lower rank scores indicate worse outcomes in the worst rank analysis.

10. Secondary Endpoint Descriptions

10.1 – Secondary Endpoint #1

Endpoint Description: Days alive and out of hospital at 24 weeks, not listed for transplant (Status 1A, 1B or 1-4) or undergoing transplant, implanted with an LVAD, maintained or started on continuous inotropic therapy for ≥ 7 days, or has had two hospital admissions for heart failure (HF), other than the index admission. The days alive and out of hospital will end on the day of the second HF readmission, if applicable, using the pre-COVID-19 population.

Response Variable Definition: Each component of the endpoint will have daily flags created indicating whether the patient met the endpoint on that specific day. Days will start at day of randomization (Day 0) and continue until a maximum of 163 (beginning of 24 week visit window). Determination of the final evaluable date will depend upon which component is under evaluation. Any data collected after 163 days post randomization will not count for this endpoint.

Days alive: If a patient died between randomization and 163 days post randomization, each day will be coded as a 0 is they were alive and will be coded as a 1 if the patient has previously died. All 163 post-randomization days will be evaluable if the patient died. If the patient had not died, the last evaluable date will be minimum of 163 days post randomization, date of Week 24 visit, date of withdrawn consent or date of loss to follow-up.

Out of hospital: If a patient was randomized while admitted to the hospital, each day the patient was in the hospital from randomization to discharge will be coded as a 1, otherwise the coded value will be a 0. For every other unplanned hospital admission, the patient will be coded as a 0 if they were not hospitalized and coded as a 1 if they were, using the admission and discharge dates as the anchors. The last evaluable date will be minimum of 163 days post randomization, date of Week 24 visit, date of withdrawn consent, date of death or date of loss to follow-up.

Not listed for transplant or undergoing transplant: If a patient either has been listed for heart transplant or received a transplant, each day will be coded as a 0 is they were not listed/transplanted and will be coded as a 1 if the patient had been listed or transplanted. The last evaluable date will be minimum of 163 days post randomization, date of Week 24 visit, date of withdrawn consent, date of death or date of loss to follow-up.

Not implanted with a LVAD: If a patient had been implanted with a LVAD, each day will be coded as a 0 is they were not implanted and will be coded as a 1 if the patient had been implanted. The last evaluable date will be minimum of 163 days post randomization, date of Week 24 visit, date of withdrawn consent, date of death or date of loss to follow-up.

Not maintained or starting continuous IV inotropes for at least 7 days: If the patient had been taking continuous IV inotropes for at least 7 days, each day from the start of inotropes (or randomization date if inotropes started prior to randomization) through the discontinuation of inotropes will be coded as a 1. If the patient does not have a discontinuation date, the assumption will be that inotropes continued to minimum of 163 days post randomization, date of Week 24 visit, date of withdrawn

consent, date of death, or date of loss to follow-up. For those days where the patient is not taking inotropes, the coded value will be 0.

Free of two heart failure hospitalizations: If the patient had two unplanned heart failure hospitalizations, each day from the second HF admission will be coded as a 1. Every day prior to the second HF admission will be coded as a 0. Coding will continue through a minimum of 163 days post randomization, date of Week 24 visit, date of withdrawn consent, date of death, or date of loss to follow-up.

Composite endpoint of event free days: Using each of the endpoint components above, determine the maximum value for the coded value for each of Day 0 through 163. If no endpoints met, the patient met the criteria for an event free day.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data:To account for missing data due to right censoring, inverse probability weighted estimates will be calculated for each treatment group. These estimators adjust for the potential bias due to administratively censored data by reweighting the observed data by a function of the Kaplan-Meier estimate of the censoring distribution. The data will be partitioned from randomization (Day 0) to Day 79 and Day 80 to Day 163.

Sensitivity Analyses:
1) Instead of using the beginning of the Week 12 visit window (79 days post-randomization) and Week 24 visit window (163 days post-randomization) to count event days, use the projected Weeks 12 and 24 visit dates (84 and 168 days post randomization, respectively), using the pre-COVID-19 population.
2) Re-calculate the endpoint analysis using the original ITT population.
3) Re-calculate sensitivity analysis 1) using the original ITT population.

Statistical Tests: The Kaplan-Meier estimator for the censoring distribution will be obtained by reversing the usual role of survival and censoring within PROC LIFETEST. A partitioned version of the Bang-Tsiatis estimator will be applied using PROC GENMOD in SAS. The IPW estimate using partitions at Days 79 and 163 will be used to estimate the difference between treatment groups.

Interpretation of Treatment Comparison: A lower number of days affected by the components of this composite endpoint (higher number of event free days) indicates that LCZ696 provides an improved clinical response versus Valsartan.

10.2 – Secondary Endpoint #2

Endpoint Description: Tolerability measured as number of subjects achieving a target dose of 25%, 50% or 100% of valsartan or LCZ696, using the pre-COVID-19 population.

Response Variable Definition: Due to limited documentation concerning reasons for dose reduction, four versions of this endpoint will be calculated:
1) maximum study drug dose started (including 0),
2) dose patient took for the most number of days (including 0),
3) last dose patient was taking (including 0), and
4) last dose patient was taking (excluding 0).

There are 4 ordered values possible based upon the coding of the responses. Each response will be coded to represent 0% of target (no drug), 25% of target (50 mg LCZ696/40 mg Valsartan), 50% of target (100 mg LCZ696/80 mg Valsartan) or 100% of target (200 mg LCZ696/160 mg Valsartan). The number of evaluable days will be based on time from randomization to earliest date of Week 24, Death, Consent Withdrawal, or Last Contact.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: No adjustment will be made for missing data.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: An ordinal logistic regression model (PROC LOGISTIC in SAS) will be used to estimate and statistically compare whether there is differential study drug dose achievement between the treatments.

Interpretation of Treatment Comparison: More patients achieving/tolerating higher doses indicates better tolerance of LCZ696 versus Valsartan.

10.3 – Secondary Endpoint #3

Endpoint Description: Tolerability measured as number of subjects developing hypotension (SBP ≤ 85 mmHg) with symptoms, using the pre-COVID-19 population.

Response Variable Definition: Number of subjects with a documented event of interest of symptomatic hypotension defined as systolic blood pressure ≤ 85 mmHg between Randomization and the Week 24 assessment.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: Each patient will be evaluated based on the available follow-up. No adjustment for incomplete follow-up will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: A logistic regression model (PROC LOGISTIC in SAS) will be used to estimate and statistically compare whether there is differential rate of subjects developing symptomatic hypotension between the treatments.

Interpretation of Results: A lower rate of symptomatic hypotension defined as systolic blood pressure ≤ 85 mmHg indicates better tolerance of LCZ696 arm versus Valsartan.

10.4 – Secondary Endpoint #4

Endpoint Description: Tolerability measured as number of subjects developing worsening renal function (eGFR <20 ml/min/1.73m²), using the pre-COVID-19 population.

Response Variable Definition: Number of subjects with a documented event of interest of worsening renal function defined as eGFR <20 ml/min/1.73m² between Randomization and the Week 24 assessment.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: Each patient will be evaluated based on the available follow-up. No adjustment for incomplete follow-up will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: A logistic regression model (PROC LOGISTIC in SAS) will be used to estimate and statistically compare whether there is differential rate of subjects developing worsening renal function between the treatments.

Interpretation of Results: A lower rate of developing worsening renal function defined as GFR < 20 ml/min/1.73m^2, indicates better tolerance of LCZ696 arm versus Valsartan.

10.5 – Secondary Endpoint #5

Endpoint Description: Tolerability measured as number of subjects developing moderate (> 5.5 mmol/L) or severe (≥ 6 mmol/L) hyperkalemia, using the pre-COVID-19 population.

Response Variable Definition: Number of subjects with a documented event of interest of hyperkalemia defined as potassium > 5.5 mmol/L between Randomization and the Week 24 assessment.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: Each patient will be evaluated based on the available follow-up. No adjustment for incomplete follow-up will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: A logistic regression model (PROC LOGISITIC in SAS) will be used to estimate and statistically compare whether there is differential rate of subjects developing hyperkalemia between the treatments.

Interpretation of Results: A lower rate of developing moderate or severe hypokalemia defined as potassium > 5.5 mmol/L, indicates better tolerance of LCZ696 arm versus Valsartan.

11. Tertiary Endpoint Descriptions

11.1 – Tertiary Endpoint #1

Endpoint Description: Time to death through 24 weeks, using the pre-COVID-19 population.

Response Variable Definition: Deaths occurring from the time of randomization through the Week 24 assessment. In the event the patient did not have complete follow-up through Week 24, the patient will be censored at the time of their last follow-up prior to the Week 24 assessment.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: Each patient will be evaluated based on the available follow-up. No adjustment for incomplete follow-up will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: The Cox regression model for survival data (PROC PHREG in SAS) will be used to test the statistical significance of differences in time to death between the treatments. Kaplan-Meier curves will be generated to graphically display the event rates as a function of time from randomization in each treatment.

Interpretation of Results: A lower rate of death through 24 weeks indicates lower mortality in the LCZ696 arm versus Valsartan.

11.2 – Tertiary Endpoint #2

Endpoint Description: Time to cardiovascular death through 24 weeks, using the pre-COVID-19 population.

Response Variable Definition: Site-classified cardiovascular deaths occurring from the time of randomization through the Week 24 assessment. In the event the patient did not have complete follow-up through Week 24, the patient will be censored at the time of their last follow-up prior to the Week 24 assessment.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: Each patient will be evaluated based on the available follow-up. No adjustment for incomplete follow-up will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: The Cox regression model for survival data (PROC PHREG in SAS) will be used to test the statistical significance of differences in time to cardiovascular death between the treatments. Kaplan-Meier curves will be generated to graphically display the event rates as a function of time from randomization in each treatment.

Interpretation of Results: A lower rate of cardiovascular death through 24 weeks indicates lower cardiovascular-related mortality in the LCZ696 arm versus Valsartan.

11.3 – Tertiary Endpoint #3

Endpoint Description: Time to first unplanned heart failure hospitalization through 24 weeks, using the pre-COVID-19 population.

Response Variable Definition: Unplanned heart failure hospitalizations occurring from the time of randomization through the Week 24 assessment. The event time will be set at the time of the first unplanned heart failure hospitalization. In the event the patient did not have complete follow-up through Week 24, the patient will be censored at the time of their last follow-up prior to the Week 24 assessment.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: Each patient will be evaluated based on the available follow-up. No adjustment for incomplete follow-up will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: The Cox regression model for survival data (PROC PHREG in SAS) will be used to test the statistical significance of differences in time to first unplanned heart failure hospitalization between the treatments. Kaplan-Meier curves will be generated to graphically display the event rates as a function of time from randomization in each treatment.

Interpretation of Results: A lower rate of unplanned heart failure hospitalizations through 24 weeks indicates lower heart failure hospital admission rates in the LCZ696 arm versus Valsartan.

11.4 – Tertiary Endpoint #4

Endpoint Description: Time to death or first unplanned heart failure hospitalization through 24 weeks, using the pre-COVID-19 population.

Response Variable Definition: Death or unplanned heart failure hospitalizations occurring from the time of randomization through the Week 24 assessment. The event time will be set at the time of the earliest of death or first unplanned heart failure hospitalization. In the event the patient did not have complete follow-up through Week 24, the patient will be censored at the time of their last follow-up prior to the Week 24 assessment.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: Each patient will be evaluated based on the available follow-up. No adjustment for incomplete follow-up will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: The Cox regression model for survival data (PROC PHREG in SAS) will be used to test the statistical significance of differences in time to death or first unplanned heart failure hospitalization between the treatments. Kaplan-Meier curves will be generated to graphically display the event rates as a function of time from randomization in each treatment.

Interpretation of Results: A lower rate of unplanned heart failure hospitalizations or death through 24 weeks indicates lower clinical event rates in the LCZ696 arm versus Valsartan.

11.5 – Tertiary Endpoint #5

Endpoint Description: Time to cardiovascular death or first unplanned heart failure hospitalization through 24 weeks, using the pre-COVID-19 population.

Response Variable Definition: Site-classified cardiovascular death or unplanned heart failure hospitalizations occurring from the time of randomization through the Week 24 assessment. The event time will be set at the time of the earliest of cardiovascular death or first unplanned heart failure hospitalization. In the event the patient did not have complete follow-up through Week 24, the patient will be censored at the time of their last follow-up prior to the Week 24 assessment.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: Each patient will be evaluated based on the available follow-up. No adjustment for incomplete follow-up will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: The Cox regression model for survival data (PROC PHREG in SAS) will be used to test the statistical significance of differences in time to cardiovascular death or first unplanned heart failure hospitalization between the treatments. Kaplan-Meier curves will be generated to graphically display the event rates as a function of time from randomization in each treatment.

Interpretation of Results: A lower rate of unplanned heart failure hospitalizations or cardiovascular death through 24 weeks indicates lower clinical event rates in the LCZ696 arm versus Valsartan.

11.6 – Tertiary Endpoint #6

Endpoint Description: Total number of unplanned heart failure hospital admissions through 24 weeks, using the pre-COVID-19 population.

Response Variable Definition: Number of unplanned heart failure hospitalizations between Randomization and Week 24.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: Each patient will be evaluated based on the available follow-up. No adjustment for incomplete follow-up will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: A Poisson regression model (PROC GENMOD in SAS) will be used to estimate and statistically compare whether there is differential rate of subjects experiencing unplanned heart failure hospital admissions between the treatments.

Interpretation of Results: A smaller number of unplanned heart failure hospitalizations through 24 weeks indicates a reduction in admissions in the LCZ696 arm versus Valsartan.

11.7 – Tertiary Endpoint #7

Endpoint Description: Number of subjects on continuous inotropic therapy ≥ 7 days after discharge from the index hospitalization through 24 weeks, using the pre-COVID-19 population.

Response Variable Definition: An indicator for patient taking at least 7 days of continuous inotropic therapy at any time from Randomization (or index hospital discharge if later) through Week 24.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: Each patient will be evaluated based on the available follow-up. No adjustment for incomplete follow-up will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: A logistic regression model (PROC LOGISTIC in SAS) will be used to estimate and statistically compare whether there is differential rate of subjects taking at least 7 days of continuous inotropic therapy between the treatments.

Interpretation of Results: A smaller number of patients requiring at least 7 continuous days of inotropic therapy through 24 weeks indicates an improvement in the LCZ696 arm versus Valsartan.

11.8 – Tertiary Endpoint #8

Endpoint Description: Number of subjects listed for transplant (1A, 1B or 1-4), transplanted or implanted with an LVAD through 24 weeks, using the pre-COVID-19 population.

Response Variable Definition: Number of patients listed for heart transplant, transplanted or implanted with a LVAD between Randomization and Week 24.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: Each patient will be evaluated based on the available follow-up. No adjustment for incomplete follow-up will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: A logistic regression model (PROC LOGISTIC in SAS) will be used to estimate and statistically compare whether there is differential rate of subjects meeting the endpoint between the treatments.

Interpretation of Results: A smaller number of patients requiring LVAD or heart transplant, including listing for transplant, through 24 weeks indicates an improvement in the LCZ696 arm versus Valsartan.

11.9 – Tertiary Endpoint #9

Endpoint Description: Change in eGFR levels compared to baseline. Renal function was assessed at baseline, weeks 2, 4, 8, 12, and 24, using the pre-COVID-19 population.

Response Variable Definition: Change from baseline in eGFR at Weeks, 2, 4, 8, 12, and 24.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: No adjustment for missing data will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: A mixed model (PROC MIXED in SAS) will be used to estimate and statistically compare changes in GFR between Baseline and Weeks 2, 4, 8, 12 and 24 values.

Interpretation of Results: A higher GFR indicates better renal function in the LCZ696 arm vs Valsartan.

11.10 – Tertiary Endpoint #10

Endpoint Description: Change in cystatin C levels compared to baseline. Renal function was assessed at baseline, weeks 2, 4, 8, 12, and 24, using the pre-COVID-19 population.

Response Variable Definition: Change from baseline in Cystatin C at Weeks, 2, 4, 8, 12, and 24.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: No adjustment for missing data will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: A mixed model (PROC MIXED in SAS) will be used to estimate and statistically compare changes in Cystatin C between Baseline and Weeks 2, 4, 8, 12 and 24 values.

Interpretation of Results: A lower cystatin C indicates improvement in the LCZ696 arm vs Valsartan.

11.11 – Tertiary Endpoint #11

Endpoint Description: Number of subjects with unanticipated use of IV diuretics (outpatient, ER or inpatient) through 24 weeks, using the pre-COVID-19 population.

Response Variable Definition: An indicator for patient having unanticipated use of IV diuretics (outpatient, ER or inpatient) through 24 weeks.

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization

Handling of Dropouts and Missing Data: Each patient will be evaluated based on the available follow-up. No adjustment for incomplete follow-up will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: A logistic regression model (PROC LOGISTIC in SAS) will be used to estimate and statistically compare whether there is differential rate of subjects meeting the endpoint between the treatments.

Interpretation of Results: A smaller number of patients requiring unanticipated use of IV diuretics through 24 weeks indicates an improvement in the LCZ696 arm versus Valsartan.

11.12 – Tertiary Endpoint #12

Endpoint Description: Change in AUC in the Kansas City Cardiomyopathy Questionnaire (KCCQ) compared to baseline – both for overall and clinical summary scores, using the pre-COVID-19 population.

Response Variable Definition: The KCCQ questionnaire was completed at Screening (considered Baseline for this analysis), Week 4, Week 12 and Week 24. The endpoint will be derived in a similar fashion to the primary endpoint (see 9.1).

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization, appropriate baseline value of each KCCQ score

Handling of Dropouts and Missing Data: If missing KCCQ score at Week 24, use last observation carried forward (LOCF) from previous post-Baseline time point with available KCCQ score data. No adjustment will be made for missing Baseline results.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: A general linear model (PROC GLM in SAS) will be used to test the significance of differences in the area under the curve for the each KCCQ score between the two treatment arms.

Interpretation of Results: A higher KCCQ score indicates an improved KCCQ score in the LCZ696 arm versus Valsartan.

11.13 – Tertiary Endpoint #13

[Tertiary Endpoint #13 will only assessed on the first 200 patients randomized, as generated for the Interim Analysis. A decision was made by the Executive Committee to not assay for BNP at trial completion for the remaining randomized patients.]

Endpoint Description: The log of the proportional change from baseline in the area under the curve for the ratio of NT Pro BNP/BNP compared to baseline.

Response Variable Definition: The was collected at Baseline, Week 2, Week 4, Week 8, Week 12 and Week 24. The endpoint will be derived in a similar fashion to the primary endpoint (see 9.1).

Additional Covariates in Addition to Randomized Treatment: atrial fibrillation status at time of randomization, baseline value of log(BNP) and log(NT Pro BNP).

Handling of Dropouts and Missing Data: If missing biomarker data at Week 24, use last observation carried forward (LOCF) from previous post-Baseline time point with available data. No adjustment will be made for missing Baseline results.

Sensitivity Analysis: No sensitivity analyses will be performed.

Statistical Tests: A general linear model (PROC GLM in SAS) will be used to test the significance of differences in the area under the curve for the ratio of NT Pro BNP to BNP between the two treatment arms.

Interpretation of Results: A lower value for the NT Pro BNP/BNP ratio indicates an improvement in the LCZ696 arm versus Valsartan.

12. Exploratory Endpoint Descriptions

12.1 – Exploratory Endpoint #1

Endpoint Description: A four level modified clinical composite endpoint including 1) death, 2) LVAD or Heart Transplant (including listing status of 1A, 1B or 1-4), 3) multiple HF hospital admissions, and 4) single HF admission, using the pre-COVID-19 population.

Response Variable Definition: The unmatched approach to the win ratio of Pocock will be used. In general terms, each patient will be placed into one of the hierarchical groups based on the comparison of LCZ696 versus Valsartan patients. The hierarchy for the comparisons is as follows:

(a) LCZ696 patient had death first
(b) Valsartan patient had death first
(c) LCZ696 patient had LVAD or HTP first
(d) Valsartan patient had LVAD or HTP first
(e) LCZ696 patient had multiple HF hospital admissions first
(f) Valsartan patient had multiple HF hospital admissions first
(g) LCZ696 patient had single HF hospital admission first
(h) Valsartan patient had single HF hospital admission first
(i) None of the above

Additional Covariates in Addition to Randomized Treatment: None

Handling of Dropouts and Missing Data: All patients are expected to have some data to address this endpoint. No further adjustments for incomplete or missing data will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: The win ratio approach of Pocock will be used to evaluate each endpoint. Calculation of the test statistics, p-values and confidence intervals is detailed in the Pocock manuscript (Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: A new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J*.33:176-182).

Interpretation of Results: A win ratio of 1.0 is the null value. Estimates below 1.0 indicate a worse outcome and win ratios greater than 1.0 indicate a favorable effect for the LCZ696 arm.

13. Safety analysis

13.1 – Safety Endpoint #1

Safety Endpoint #1: Comparison of serious adverse events at the level of MedDRA preferred term, using the pre-COVID-19 population.

Response Variable Definitions: The number of patients experiencing each unique serious adverse event (SAE) type based on MedDRA preferred term within body system.

Additional Covariates: None

Handling of Dropouts and Missing Data: No adjustments for missing data will be made.

Sensitivity Analysis: Re-calculate the endpoint analysis using the original ITT population.

Statistical Tests: Fisher's mid-p will be calculated for each serious adverse event based upon the unique MedDRA preferred term within a body system.

Interpretation of Results: Lower event rates indicate a better outcome for LCZ696 arm versus Valsartan.

14. Interim Analyses

Interim data analysis for efficacy was conducted at the request of the National Heart Lung and Blood Institute (NHLBI). This analysis was performed after 200 patients completed their follow-up and their biomarkers were processed.

Haybittle-Peto methods were used to assess the primary endpoint, using alpha of 0.001, to evaluate whether the trial could be stopped early due to efficacy.

Conditional power was calculated under different scenarios for the primary and secondary endpoints.

Safety data was assessed quarterly by the Data and Safety Monitoring Board (DSMB) based on the reporting of adverse events and otherwise reviewed monthly by the DSMB Chair. There were no pre-specified guidelines for determining stopping rules due to a safety concern; the clinical opinion from the DSMB deliberations will be sole determinant.

15. Subgroup of Interest

Selected analyses will be performed on the following subgroups: a) patients with and without atrial fibrillation, b) the subgroup of gender will be included to satisfy the NHLBI Inclusion policy, and c) the subgroup of racial or ethnic minority will be included to satisfy the NHLBI Inclusion policy. Models will either adjust for presence of subgroup or will be performed in each subgroup, as appropriate.