Statistical Analysis Plan J3E-MC-EZDB (1)

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of LY3540378 in Adults with Worsening Chronic Heart Failure with Preserved Ejection Fraction (HFpEF)

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Statistical Analysis Plan (J3E-MC-EZDB): A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of LY3540378 in Adults with Worsening Chronic Heart Failure with Preserved Ejection Fraction (HFpEF)

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Protocol Number: J3E-MC-EZDB

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Brief Title: Efficacy and Safety of LY3540378 in Adults with Worsening Chronic Heart Failure with Preserved Ejection Fraction

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Version history

This Statistical Analysis Plan (SAP) for Study J3E-MC-EZDB is based on the protocol (b) dated 09 April 2024.

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	See date on Page 1	Not Applicable	Original version

1. Introduction

There are no changes to the analyses described in the protocol.

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To demonstrate that LY3540378 administered SC QW is superior to placebo for improving atrial myopathy in participants with worsening chronic HFpEF	Change from baseline to Week 26 in LARS
Secondary	
To compare the effect of LY3540378 administered SC QW on participants with worsening chronic HFpEF	Change from baseline to Weeks 12 in LARS Change from baseline to Weeks 12 and 26 in • Log-transformed NT-proBNP[a] • LAEDVI • LAESVI • eGFR (CKD-EPI Creatinine-Cystatin equation [Inker et al. 2021]) • log-transformed serum creatinine[a], and • log-transformed cystatin-C[a]
To assess safety and tolerability of LY3540378 administered SC QW	• AE overall • safety topics of special interest
Tertiary	
To compare the effect of LY3540378 administered SC QW on participants with worsening chronic HFpEF	• Change from baseline to Weeks 12 and 26 in o LA emptying fraction o LVGLS o E/A o E/e' o LVM (LVMI) o log-transformed high sensitivity troponin, (hs-cTnT)[a] o NYHA class, and o log-transformed BNP[a] • Change from baseline to the average of Week [redacted] and Week 26 in log-transformed NT-proBNP • Blood pressure and pulse rate

Objectives	Endpoints

Clinical outcome events of HF	Incidence of
	• All deaths (CV and non-CV)
	• HF event:
	  ○ hospitalized (HF hospitalization) and
	  ○ non-hospitalized HF events (urgent outpatient visits, unscheduled office, or emergency visit for HF)

Change in outpatient hemodynamic CV medications	Change in the dosing of • diuretics (loop and thiazide) • RAAS inhibitor • SGLT-2i • Beta blockers • ARNI, and • MRA

To assess the effect of LY3540378 on patient-reported outcomes	Change from baseline through Week 26 of
	• Severity of CCI [redacted]
	• PGIS-HF Overall Health
	• PGIC-HF Overall Health
	• PGIS-HF Symptom Severity
	• PGIC-HF Symptom Severity, and
	• KCCQ
	  ○ Total Symptom Score
	  ○ Clinical Summary Score, and
	  ○ Overall Summary Score

To assess presence of anti-LY3540378 antibodies	ADAs against LY3540378 including • treatment-emergent ADAs, and • neutralizing antibodies
To assess LY3540378 PK and the relationship between LY3540378 dose or exposure and clinical endpoints and potential participant factors that may influence these relationships	PK parameters of LY3540378 (C_{max}, AUC). Dose or exposure-response analyses for key efficacy and safety endpoints

Abbreviations: ADA = anti-drug antibody; AE = adverse event; ARNI = angiotensin receptor neprilysin inhibitor; BNP = brain natriuretic peptide; CV = cardiovascular; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; LA = left atrium; LAEDVI = left atrial end-diastolic volume index; LAESVI = left atrial end-systolic volume index; LARS = left atrial reservoir strain; LVGLS = left ventricular global longitudinal strain; LVM = left ventricular mass; LVMI = left ventricular mass index; MRA = mineralocorticoid receptor antagonists; CCI [redacted] NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PGIC-HF = Patient Global Impression of Change – Heart Failure; PGIS-HF = Patient Global Impression of Status – Heart Failure; PRO = patient-reported outcome; RAAS = Renin-angiotensin-aldosterone system; SC = subcutaneous; SGLT-2i = sodium-glucose cotransporter-2 inhibitor; QW = weekly.

a: For NTproBNP, serum creatinine, cystatin-C, BNP and hs-cTnT, observations will be log-transformed first prior to conducting analysis. Then results will be back-transformed to percentage difference in the original scale. Refer to Section 4.1 for details.

Primary estimand

The primary clinical question of interest is

> What is the treatment difference in LARS change from baseline after 26 weeks of treatment in study participants who would have completed the treatment period?

Efficacy estimand attributes

Table EZDB.1.1 describes the efficacy estimand attributes.

Table EZDB.1.1. Attributes for Efficacy Estimand of Primary Endpoint

Efficacy Estimand Attribute	Description
Population	Participants who meet the inclusion criteria. Further details can be found in Sections 5 and 9. of the protocol J3E-MC-EZDB(b).
Endpoint	Change from baseline in LARS at Week 26.
Treatment condition	The randomized treatment with allowance for dose modification based on hypotension and temporary discontinuation for safety (Section 6.5 and 7.1.4 of the protocol J3E-MC-EZDB(b)).
Population-level summary	Difference in mean absolute changes in LARS at Week 26 between LY3540378 and placebo.

Abbreviations: LARS = left atrial reservoir strain; TD = temporary discontinuation.

Intercurrent events

The intercurrent event, “permanent discontinuation of intervention,” is handled by the hypothetical strategy. The potential outcome of interest is the response in the efficacy measurement if participants adhere to the randomized treatment.

Rationale for the efficacy estimand

This Phase 2 study aims to study the efficacy of LY3540378 under the ideal condition that all participants adhere to the randomized treatment.

Estimand(s) for Secondary Objectives

The same estimand for the primary objective will be used for the following efficacy endpoints for the secondary objective:

- Change from baseline to Weeks 12 in LARS, and
- Change from baseline to Weeks 12 and 26 in
  - Log-transformed NT-proBNP
  - LAEDVI
  - LAESVI
  - eGFR (calculated by creatinine and cystatin-C)
  - log-transformed serum creatinine, and
  - log-transformed cystatin-C

Unless specified otherwise, safety and tolerability assessments will be guided by an estimand comparing safety of LY3540378 doses with placebo irrespective of adherence to study intervention, including data collected during the treatment period and safety follow-up from all randomized participants who are exposed to at least 1 dose of study drug, regardless of adherence of study drug.

Estimand(s) in Exploratory Analyses

The "treatment policy" estimand, which represents the efficacy irrespective of adherence to study intervention, will also be used to compare the efficacy of LY3540378 doses with placebo for primary and secondary endpoints in the exploratory analyses, which includes:

Change from baseline to Weeks 12 and 26 in

- LARS
- log-transformed NT-proBNP
- LAEDVI
- LAESVI
- eGFR (calculated by creatinine and cystatin-C)
- log-transformed serum creatinine, and
- log-transformed cystatin-C

The clinical question of interest in the exploratory analyses is: What is the intervention difference in change from baseline at Week 12 and 26 of the primary and secondary endpoints in participants who meet the inclusion criteria regardless of treatment discontinuation for any reason?

Treatment policy estimand attributes

Table EZDB.1.2 describes the treatment policy estimand attributes.

Table EZDB.1.2. Attributes of Treatment Policy Estimand of Primary and Secondary Endpoints

Efficacy Estimand Attribute	Description
Population	Participants who meet the inclusion criteria. Further details can be found in Sections 5 and 9. of the protocol J3E-MC-EZDB(b).
Endpoints	Change from baseline to Weeks 12 and 26 in • LARS • log-transformed NT-proBNP • LAEDVI • LAESVI • eGFR (CKD-EPI Creatinine-Cystatin equation [2021]) • log-transformed serum creatinine[a], and • log-transformed cystatin-C[a]
Treatment condition	The randomized treatment with allowance for dose modification based on hypotension and temporary discontinuation for safety (Section 6.5 and 7.1.4 of the protocol J3E-MC-EZDB(b)).
Population-level summary	Difference in mean changes between LY3540378 and placebo[a].

Abbreviations: ADA = anti-drug antibody; AE = adverse event; ARNI = angiotensin receptor neprilysin inhibitor; BNP = brain natriuretic peptide; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CV = cardiovascular; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; LA = left atrium; LAEDVI = left atrial end-diastolic volume index; LAESVI = left atrial end-systolic volume index; LARS = left atrial reservoir strain; LVGLS = left ventricular global longitudinal strain; LVM = left ventricular mass; LVMI = left ventricular mass index; MRA = mineralocorticoid receptor antagonists; CCI NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PGIC-HF = Patient Global Impression of Change – Heart Failure; PGIS-HF = Patient Global Impression of Status – Heart Failure; PRO = patient-reported outcome; RAAS = Renin-angiotensin-aldosterone system; SC = subcutaneous; SGLT-2i = sodium-glucose cotransporter-2 inhibitor; QW = weekly. LARS = left atrial reservoir strain; TD = temporary discontinuation.

[a] For NTproBNP, serum creatinine and cystatin-C, observations will be log-transformed first prior to conducting analysis. Then results will be back-transformed to percentage difference in the original scale. Refer to Section 4.1 for details

Intercurrent events

The intercurrent event, “permanent discontinuation of intervention,” is handled by the treatment policy strategy, meaning all the observed values for the variable of interest are used regardless of whether or not the intercurrent event occurs.

Rationale for the treatment policy estimand

This estimand aims to study the efficacy of LY3540378 that reflects the real-life behavior of the target population.

1.2. Study Design

Study EZDB is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study that will investigate the effects of treatment with LY3540378 compared with placebo on participants with worsening chronic HFpEF.

For participants who joined study before amendment (b), they are randomized 1:1:1:1 to the following intervention groups:

- LY3540378 25 mg SC QW
- LY3540378 50 mg SC QW
- LY3540378 100 mg SC QW, and
- Placebo.

For participants who joined study after amendment (b) being active, participants will be randomized 1:2:2:2 to the above intervention groups.

Intervention administration is by subcutaneous injection, and dosing will occur every week.

The maximum total duration of study participation for each participant, including screening and safety follow-up periods, is approximately CCI weeks, across the following study periods:

- Screening: CCI
- Double-Blind Treatment: 26 weeks, and
- Safety Follow-Up: CCI .

Figure EZDB.1.1. Illustration of study design for clinical protocol J3E-MC-EZDB.

2. Statistical Hypotheses

The primary objective is to demonstrate that LY3540378 administered SC QW is superior to placebo for change from baseline in LARS at Week 26 in participants with worsening chronic HFpEF. Thus, the null hypothesis to be tested in relation to the primary estimand is as follows:

- Null hypothesis: LY3540378 is not different from placebo with respect to change from baseline in LARS at Week 26.

The null hypotheses corresponding to the secondary estimands are as follows:

- LY3540378 is not different from placebo with respect to change from baseline to Week 12 in LARS.
- LY3540378 is not different from placebo with respect to change from baseline to Week 12 or Week 26 in:
    - log-transformed NT-proBNP
    - LAEDVI
    - LAESVI
    - eGFR (calculated by creatinine and cystatin-C)
    - log-transformed serum creatinine, and
    - log-transformed cystatin-C

2.1. Multiplicity Adjustment

No adjustment for multiplicity will be performed.

3. Analysis Sets

This table defines the analysis population and datasets for the purposes of analysis.

Participant Analysis Set	Description
Screened	All participants who signed informed consent.
Randomized	All participants who are randomly assigned to a treatment arm.
Efficacy Analysis Set (EAS)	Data obtained during the treatment period from all randomly assigned participants who are exposed to at least 1 dose of intervention. Participants from site 86127 will be excluded. Excludes data after permanent discontinuation of intervention. Participants will be included in the treatment group to which they were randomly assigned.
Full Analysis Set (FAS)	Data obtained during the treatment period from all randomly assigned participants who are exposed to at least 1 dose of intervention, regardless of adherence to intervention. Participants from site 86127 will be excluded. Participants will be included in the treatment group to which they were randomly assigned.
Safety Analysis Set (SS)	Data obtained during the treatment period plus safety follow-up from all randomly assigned participants who are exposed to at least 1 dose of intervention, regardless of adherence to intervention. Participants will be included in the treatment group to which they were randomly assigned.

4. Statistical Analyses

4.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or its designee. Some analyses and summaries described in this analysis plan may not be conducted if not warranted by data (for example, few events to justify conducting an analysis). Additional analyses of the data may be conducted as deemed appropriate.

Unless otherwise noted, tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval (CI) will be calculated at 95% 2-sided. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10.

All participants from site 86127 will be excluded from the analysis for primary and secondary objectives as the site was terminated following the identification of a serious and egregious breach of protocol. All participants in the study were deemed not to meet key inclusion criteria 2. Detailed information was documented in the 86127 Serious Breach Assessment 2 02 Nov 2023 in eTMF.

Unless otherwise specified, the efficacy analysis will be conducted using Efficacy Analysis Set (EAS) and the safety analysis will be conducted using Safety Analysis Set (SS).

Unless stated otherwise, statistical summaries and analyses will be conducted based on planned randomized treatment group (Placebo, LY3540378 25 mg, LY3540378 50 mg and LY3540378 100 mg, regardless of the actual treatment(s) received by the participant due to any dose modification. The evaluation of the efficacy and safety endpoints will be conducted for LY3540378 25 mg, LY3540378 50 mg and LY3540378 100 mg and compared with placebo.

The primary estimand (a precise definition of the treatment effect to be estimated) of interest in comparing efficacy of LY3540378 doses with placebo is the “efficacy estimand” (Section 1.1). The primary efficacy assessment, guided by the “efficacy estimand” will be conducted using the EAS. A restricted maximum likelihood-based, mixed-effect model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables. All the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The model for primary efficacy endpoint of change from baseline in LARS will include Change from baseline in LARS as the dependent variable. Independent variables include the fixed class effects of treatment group (LY 25 mg, LY 50 mg, LY 100 mg and placebo), visit, treatment-by-visit interaction, gender (male, female), continuous baseline value of LARS, stratification strata defined by region (North America, Latin America, Europe and other countries, Asia) and atrial fibrillation or atrial flutter on the screening ECG (Yes, No), treatment-by-baseline interaction, treatment-by-stratum interaction. An unstructured covariance structure will be used to model the within-participant errors. If this analysis fails to converge, the following covariance structures will be tested in order:

- Heterogeneous toeplitz
- Heterogeneous autoregressive(1)

- Heterogeneous compound symmetry
- Toeplitz
- Autoregressive(1), and
- Compound symmetry.

The first covariance structure that converges will be used. Comparisons of difference in LARS change from baseline for each treatment group of LY3540378 versus placebo reference group will be made by using contrasts of LS means.

Patients in the 100 mg group are allowed to lower the dose level to 50 mg (Section 6.5 of the protocol). For the primary and secondary endpoints, an additional analysis will be conducted to pool the two highest doses (50 mg and 100 mg) together and compare with placebo group. The same above statistical model will be used as the primary analysis except that the fixed class effects will be 25 mg, pooled 50/100 mg, and placebo groups.

Baseline is defined as the last nonmissing measurement recorded on or before the randomization visit, prior to the first dose of intervention, unless otherwise specified. Table EZDB.4.2 summarizes the definition of baseline, postbaseline, and patient population for different endpoints.

Data may exist at visits where the variable was not scheduled to be collected. In these situations, data from the early discontinuation visit that does not correspond to the planned collection schedule will be excluded from the MMRM, analysis of covariance (ANCOVA), or logistic regression analysis.

For laboratory values, both conventional (CN) and International System of Units (SI) units will be presented.

For continuous measures which does not need log transformation, summary statistics will include sample size, mean, standard deviation (SD), minimum, and maximum for both the actual and the change from baseline measurements. LS means and standard errors derived from the analysis models will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs for the treatment differences, along with the p-values for the treatment comparisons.

For continuous variables that are log-transformed due to skewed distribution (e.g. NTproBNP, BNP, serum creatinine, cystatin-C and hs-cTnT, UACR), summary statistics will include sample size, median, interquartile range (IQR), minimum and maximum for actual value. In addition, log transformation will be applied and then summary statistics including mean and SD will be conducted on log-transformed values. Statistical model will be applied on the log-transformed values. LS means, standard errors, treatment difference LS means and 95% CIs for the treatment differences for the log-transformed variable will be derived and displayed. Then treatment difference and corresponding 95% CIs will be subsequently back-transformed to percentage difference in the original scale. Table EZDB.4.1 lists the back-transformation in details.

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Table EZDB.4.1. Back-transformation for Analysis Results of Log-transformed Variables

Quantity		Change from baseline in log-transformed value	Back-transformation to percentage change in original scale
Within Treatment group k	Estimate	$\hat{\mu}_k$	$[\exp(\hat{\mu}_k) - 1] \times 100\%$
	SE	$\widehat{SE}_k$	NR
	95% CI	$(LL_{\mu,k}, UL_{\mu,k})$	$([\exp(LL_{\mu,k}) - 1] \times 100\%, [\exp(UL_{\mu,k}) - 1] \times 100\%)$
Between-Treatment Difference (Treatment k vs. reference placebo r)	Estimate	$\hat{\mu}_{k\ vs\ r}$	$[\exp(\hat{\mu}_{k\ vs\ r}) - 1] \times 100\%$
	SE	$\widehat{SE}_{k\ vs\ r}$	NR
	p-value	$p_{\mu,k\ vs\ r}$	$p_{\mu,k\ vs\ r}$
	95% CI	$(LL_{\mu,k\ vs\ r}, UL_{\mu,k\ vs\ r})$	$([\exp(LL_{\mu,k\ vs\ r}) - 1] \times 100\%, [\exp(UL_{\mu,k\ vs\ r}) - 1] \times 100\%)$

Abbreviations: CI = confidence interval; NR = not reported; SE = standard error.

For categorical measures, summary statistics will include sample size, frequency, and percentages. A logistic regression model may be used to examine the treatment difference in binary efficacy outcomes with missing endpoints imputed. Fisher's exact test or Pearson's chi-square test will be used for treatment comparisons in other categorical outcomes.

Details about the analyses regarding demographic and baseline characteristics, historical illnesses, and preexisting conditions, treatment compliance, concomitant medications, and important protocol deviations can be found in Appendices 1 through 5 (Section 6.1 through Section 6.5, respectively.

End of study participation for a participant will be the earliest of date of death or date of withdrawal from further participation in the study, or date of safety follow-up visit (Visit 802). For participants considered to be lost-to-follow-up, end of study participation will be the date of lost-to-follow-up reported by the investigator. Participant data included in the database after the last date of study participation will be excluded from statistical analysis.

Statistical treatment comparisons will only be performed between LY3540378 and placebo. Because the trial is not adequately powered to detect differences among LY3540378 doses, comparisons across LY3540378 doses will not be performed unless otherwise specified.

Not all analyses described in this SAP will necessarily be included in the clinical study report (CSR). Any analysis described in this SAP and not provided in the CSR will be available upon request.

Table EZDB.4.2. Baseline and Postbaseline Definitions and Patient Population by Type of Analysis

Analysis Type	Participant Population	Baseline Observations	Postbaseline Observations
26 weeks treatment period plus 4 weeks safety follow-up			
ECHO parameters listed in primary, secondary and tertiary objectives, including LARS, LAEDVI, LAESVI, LA emptying fraction, LVGLS, E/A, E/e', LVM and LVMI (MMRM, EAS for efficacy estimand)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation prior to permanent discontinuation of study drug. Participants from site 86127 will be excluded.	Visit 1	Visit 16, Visit 24 prior to permanent discontinuation of study drug
ECHO parameters listed in primary, secondary and tertiary objectives, including LARS, LAEDVI, LAESVI, LA emptying fraction, LVGLS, E/A, E/e', LVM and LVMI (MMRM, FAS for treatment policy estimand)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation. Participants from site 86127 will be excluded.	Visit 1	Visit 16, Visit 24 with imputation for participants who had missing values at Visits 16 and 24
Biomarker parameters listed in the secondary objectives, including NT-proBNP, eGFR (CKD-EPI creatinine-cystatin equation [2021]), serum creatinine and cystatin-C (MMRM, EAS for efficacy estimand)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation prior to permanent discontinuation of study drug. Participants from site 86127 will be excluded.	Last nonmissing measurement recorded on or before the randomization visit (Visit 2), prior to the first dose of intervention	Visit 3, 5, 10, 14, 16, 18, 22, 24 prior to permanent discontinuation of study drug
Biomarker parameters listed in the secondary objectives, including NT-proBNP, eGFR (CKD-EPI creatinine-cystatin equation [2021]), serum creatinine, cystatin-C (MMRM, FAS for treatment policy estimand)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation. Participants from site 86127 will be excluded.	Last nonmissing measurement recorded on or before the randomization visit (Visit 2), prior to the first dose of intervention	Visit 3, 5, 10, 14, 16, 18, 22, 24 with imputation for participants who had missing values at these visits
Biomarker parameters listed in the tertiary objectives, including BNP, high sensitivity troponin (hs-cTnT) (MMRM, EAS for efficacy estimand)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation prior to permanent discontinuation of study drug. Participants from site 86127 will be excluded.	Last nonmissing measurement recorded on or before the randomization visit (Visit 2), prior to the first dose of intervention	Visit 3, 5, 10, 14, 16, 18, 22, 24 prior to permanent discontinuation of study drug

Analysis Type	Participant Population	Baseline Observations	Postbaseline Observations
Average of CCI and CCI in log-transformed NT-proBNP (ANCOVA, EAS)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation prior to permanent discontinuation of study drug. Participants from site 86127 will be excluded.	Last nonmissing measurement recorded on or before the randomization visit (Visit 2), prior to the first dose of intervention	Visit 22 and 24
NYHA class (shift analysis, EAS)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation prior to permanent discontinuation of study drug. Participants from site 86127 will be excluded.	Last nonmissing measurement recorded on or before the randomization visit (Visit 2), prior to the first dose of intervention	Visit 16 and 24
KCCQ scores (MMRM, EAS)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation prior to permanent discontinuation of study drug. Participants from site 86127 will be excluded.	Last nonmissing measurement recorded on or before the randomization visit (Visit 2), prior to the first dose of intervention	Visit 16 and 24
Severity of CCI (MMRM, EAS)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation prior to permanent discontinuation of study drug. Participants from site 86127 will be excluded.	Last nonmissing measurement recorded on or before the randomization visit (Visit 2), prior to the first dose of intervention	Visit 4, 11, 14, 16, 18, 20, 22 and 24
Treatment-Emergent Adverse Events (SS)	All randomized participants who are exposed to at least 1 dose of study drug. The baseline period is defined as the start of screening and ends prior to the first dose of study drug (Visit 2).	The baseline period is defined as the start of screening and ends prior to the first dose of study drug (Visit 2).	Starts after the first dose of study drug and end of the study period.

Analysis Type	Participant Population	Baseline Observations	Postbaseline Observations
Treatment-Emergent Abnormal Labs (SS)	All randomized participants who are exposed to at least 1 dose of study drug who have a normal baseline (with respect to the direction being analyzed) and a postbaseline observation	Baseline will be all scheduled and unscheduled measurements recorded during the baseline period as defined above (1.1).	Postbaseline will be defined as above (1.1). All scheduled and unscheduled measurements will be included.
Treatment-Emergent Abnormal Vital Signs (SS)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation	The last scheduled non-missing assessment recorded prior to the first dose of study treatment during the baseline period defined above (1.1).	Postbaseline will be defined as above (1.1). Only scheduled visits will be included. The early discontinuation visits are considered scheduled visits.
Change from Last Baseline for Labs (SS)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation	The last scheduled non-missing assessment recorded prior to the first dose of study treatment during the baseline period defined above (1.1).	Postbaseline will be defined as above (1.1). Only scheduled visits will be included. The early discontinuation visits are considered scheduled visits.
Change from Last Baseline for Blood Pressure and Pulse Rate (SS)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation	Average of triplicate VS measurements recorded on the randomization visit, prior to the first dose of intervention	Postbaseline will be defined as above (1.1). Only scheduled visits with triplicates blood pressure and pulse rate measurements will be included. The early discontinuation visits are considered scheduled visits.
Immunogenicity (SS)	All randomized participants who are exposed to at least 1 dose of study drug and have a baseline and at least 1 post-baseline observation.	Baseline is defined as predose collection at Visit 2.	Postbaseline will be defined as above (1.1). Only scheduled visits will be included. The early discontinuation visits are considered scheduled visits.

Abbreviations: BNP = brain natriuretic peptide; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; LA = left atrium; LAEDVI = left atrial end-diastolic volume index; LAESVI = left atrial end-systolic volume index; LARS = left atrial reservoir strain; LVGLS = left ventricular global longitudinal strain; LVM = left ventricular mass; LVMI = left ventricular mass index; MRA = mineralocorticoid receptor antagonists; CCI [redacted]; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PGIC-HF = Patient Global Impression of Change – Heart Failure; PGIS-HF = Patient Global Impression of Status – Heart Failure; PRO = patient-reported outcome.

Note: for the continuous analysis of clinical laboratory tests, unscheduled measurements are excluded from analysis to reduce bias (Computational Science Symposium Development of Standard Scripts and Programming Working Group 2013 [WWW]). The early discontinuation (ED) visits are considered scheduled visits.

4.2. Participant Dispositions

A listing and summary of study disposition for all randomized participants will be provided at the primary database lock and final database lock, respectively. Frequency counts and percentages of all participants screened, randomized, and receiving at least 1 dose of study drug will be presented by treatment groups. A listing and summary of randomized participants not receiving study drug will be provided. All participants who discontinue the study and/or study drug will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed and summarized by treatment groups.

4.3. Primary Endpoint Analysis

The primary efficacy assessment, guided by the "efficacy estimand," will be conducted using the EAS. For the "efficacy estimand," the hypothetical strategy is used to handle the intercurrent event (permanent discontinuation of study drug), so only data collected before the occurrence of any such intercurrent events will be used in the MMRM estimation (Section 4.1). Through the MMRM, the potential efficacy measures (after the intercurrent events) had participants not experienced intercurrent events will be implicitly imputed. The primary efficacy comparison will be based on the contrast between each treatment group of LY3540378 and placebo at Week 26 (Visit 24) from the MMRM analysis of change from baseline in LARS using the EAS. (Section 4.1). The analysis model and selection of covariance structure is described in Section 4.1. Treatment comparisons will be performed for the primary objective at the full significance level of 0.05.

4.3.1. Definition of Endpoint

The primary efficacy measure will be change in LARS from baseline to Week 26. The change in LARS at each nominal visit is defined as:

post baseline LARS [%] – baseline LARS [%].

4.3.2. Main Analytical Approach

Change from baseline in LARS will be analyzed using the MMRM model for the "efficacy estimand" as described in Section 4.1.

4.3.3. Supplemental Analyses

Analysis for pooled 50 and 100 mg

Since patients in the 100 mg group are allowed to lower the dose level to 50 mg (Section 6.5 of the protocol). An additional analysis will be conducted using efficacy estimand and pooling the two highest doses (50 mg and 100 mg) together and compare with placebo group. The same statistical approach will be used except that the fixed class effects will be 25 mg, pooled 50/100 mg, and placebo groups.

Treatment Policy Estimand

A supplemental estimand, "treatment-policy estimand" (Section 1.1), will be conducted using data in the FAS.

Treatment-policy estimand is defined as the treatment difference in the mean change in LARS from baseline at CCI between LY3540378 and placebo for the study target population with intercurrent events (ICEs) handled by treatment policy strategy. To estimate the "treatment-policy estimand", multiple imputation will be used to impute the corresponding missing potential outcome according to the following table according the scenarios of missingness:

Scenarios	**Assumption for Missingness**	**Methods to Handle Missing Values at Endpoint**
Participant has ICE (permanent discontinuation from study treatment)	Missing not at random. Considers that these participants could not adhere to their assigned treatment and may not benefit from the assigned treatment.	Missing values will be imputed using participants in the same treatment arm with similar intercurrent events but non-missing values (retrieved dropout imputation). In cases where there are not enough retrieved dropouts to provide a reliable imputation model, will impute the missing data using the jump-to-reference (placebo) imputation approach.
Participant has missing values without ICEs	Missing at random	Missing values will be imputed using all non-missing data from the same treatment arm.

Change from baseline in LARS will be analyzed using MMRM model (Section 4.1). The comparison will be based on the contrast between each treatment group of LY3540378 and placebo at CCI (Visit 24) from the MMRM analysis of change from baseline in LARS using the FAS. In addition, the comparison will also be conducted between pooled 50/100 mg and placebo. The same statistical approach will be used except that the fixed class effects will be 25 mg, pooled 50/100 mg, and placebo groups.

4.4. Secondary Efficacy Endpoints Analysis

The secondary estimands are described in (Section 1.1). The efficacy analyses for the secondary endpoints will use the EAS and MMRM analysis described in Section 4.1. Decision will be guided by the 2-sided p-values in each objective.

4.4.1. Secondary Efficacy Endpoints

4.4.1.1. Definition of Endpoint(s)

Secondary efficacy endpoints include:Change from baseline to CCI in LARSChange from baseline to CCI in the following parameters:Log-transformed NT-proBNP

- LAEDVI
- LAESVI
- eGFR (CKD-EPI creatinine-cystatin equation [2021])
- serum creatinine, and

- cystatin-C.

The change for each of the parameters at each nominal visit is defined in Table EZDB.4.3.

Table EZDB.4.3. Definition of Change from Baseline in Secondary Endpoints

Parameter	Calculation of change from baseline at each nominal visit
Log-transformed NTproBNP[a] NTproBNP[a]	post baseline log(NTproBNP[pg/mLng/L]) – baseline log(NTproBNP[pg/mLng/L])
LAEDVI	post baseline LAEDVI[mL/m^{2}mL/m^2] – baseline LAEDVI[mL/m^{2}mL/m^2], LAEDVI = LAEDV[mL] / BSA[m^{2}m^2], BSA[m^{2}m^2] = $0.007184 \times height[cm]^{0.725} \times weight(kg)^{0.425}$, height use value at Visit 1, weight use value at Week 12 (Visit 16) and Week 26 (Visit 24), respectively
LAESVI	post baseline LAESVI[mL/m^2] – baseline LAESVI[mL/m^2], LAESVI = LAESV[mL] / BSA[m^2], BSA is same as that in LAEDVI
eGFR	post baseline eGFR[mL/min/1.73m^{2}mL/min/1.73 m^2] – baseline eGFR[mL/min/1.73m^{2}mL/min/1.73 m^2]
Log-transformed serum creatinine	post baseline log(creatinine[mg/dLmg/dL]) – baseline log(creatinine [mg/dLmg/dL])
Log-transformed cystatin-C[a]	post baseline log(creatinine[mg/Lmg/L]) – baseline log(creatinine [mg/Lmg/L])

Abbreviations: BSA = body surface area.

[a] For NTproBNP, serum creatinine and cystatin-C, observations will be log-transformed first prior to conducting analysis. Then results will be back-transformed to percentage difference in the original scale. Refer to Section 4.1 for details.

For NTproBNP, serum creatinine, cystatin-C, BNP and hs-cTnT, observations will be log-transformed first prior to conducting analysis. Then results will be back-transformed to percentage difference in the original scale. Refer to Section 4.1 for details.

For NTproBNP, serum creatinine, cystatin-C, BNP and hs-cTnT, observations will be log-transformed first prior to conducting analysis. Then results will be back-transformed to percentage difference in the original scale. Refer to Section 4.1 for details.a: For NTproBNP, serum creatinine, cystatin-C, BNP and hs-cTnT, observations will be log-transformed first prior to conducting analysis. Then results will be back-transformed to percentage difference in the original scale. Refer to Section 4.1 for details

For NTproBNP, serum creatinine, cystatin-C, BNP and hs-cTnT, observations will be log-transformed first prior to conducting analysis. Then results will be back-transformed to percentage difference in the original scale. Refer to Section 4.1 for details.

For NTproBNP, serum creatinine and cystatin-C, the definition of endpoint is based on log-transformed values. Refer to Section 14.1 and Table EZDB.4.1 for analysis details of variables which needs log-transformation.

4.4.1.2. Main Analytical Approach

The analysis of the secondary efficacy endpoints will be conducted using MMRM model described in Section 4.1. Refer to Table EZDB.4.2 for the definition of population, baseline and postbaseline for each of secondary efficacy endpoints.

4.4.1.3. Supplementary Analyses

Analysis for pooled 50 and 100 mg

An additional analysis will be conducted to 50 mg and 100 mg together and compare with placebo group. The same statistical approach will be used except that the fixed class effects will be 25 mg, pooled 50/100 mg, and placebo groups.

Treatment Policy Estimand

A supplemental estimand, “treatment-policy estimand” (Section 1.1), will be conducted for each of the secondary efficacy endpoint using data in the FAS. Same approach as the treatment-policy estimand in Section 4.3.3 will be applied.

4.5. Tertiary Endpoints Analysis

Unless otherwise specified, analyses for tertiary and exploratory endpoint will be conducted for EAS. Decision will be guided by the 2-sided p-values in each objective.

4.5.1. Tertiary Endpoints in Selected ECHO Parameters, Lab Variables and Patient Reported Outcomes

For ECHO parameters, lab variables and patient reported outcomes listed in the tertiary endpoints, the definitions of baseline, postbaseline and patient populations are described in Table EZDB.4.2. For variables which distributions are skewed and need log transformation, refer to Section 4.1 and Table EZDB.4.1 for the detailed analysis approach. Detailed analysis approaches for the tertiary endpoints are described in Table EZDB.4.4.

Table EZDB.4.4. Tertiary Endpoints Analysis

Objectives	Relative to the efficacy measure	Endpoint definition	Analysis conducted
To compare the effect of LY3540378 administered SC QW on participants with worsening chronic HFpEF	Change from baseline to CCI in: LA emptying fraction (LAEF), LVGLS, E/A, E/e', LVM, LVMI	LAEF = (LAEDV – LAESV) / LAEDV × 100%, LVMI = LVM / BSA, For each ECHO parameter, change from baseline = post baseline value – baseline value	Same MMRM model as that for the primary estimand in Section 4.1. LSM estimates with 95% CIs for Week 12 and 26 will be plotted by study treatment and by Week.
	Change from baseline to CCI in BNP, and hs-cTnT	log(BNP post basline) – log(BNP baseline) log(hs-cTnT) – log(hs-cTnT)	Same MMRM model as in Section 4.1 will be applied. Refer to Section 4.1 and Table EZDB.4.1 for analysis details of variables which needs log-transformation.LSM estimates with 95% CIs through Week 26 will be plotted by study treatment.
	Change from baseline to the average of CCI and CCI in log-transformed NT-proBNP	(log(NTproBNP at Week 26) + log(NTproBNP at Week 24)) / 2 - log(NTproBNP at baseline)	ANCOVA model will be applied. Model includes fixed class effect of treatment groups (LY 25 mg, LY 50 mg, LY 100 mg and placebo). Additional covariates include stratification strata defined by regions (North America, Latin America, Europe and other countries, Asia) and atrial fibrillation or atrial flutter on the screening ECG (Yes, No), gender (male, female) and continuous covariate of baseline log(NTproBNP) value. The save ANCOVA model will also be conducted for comparison between pooled 50/100mg and placebo. The only difference in the ANCOVA model is the fixed class effects being 25 mg, pooled 50/100 mg, and placebo groups.

Objectives	Relative to the efficacy measure	Endpoint definition	Analysis conducted
			LSM estimates with 95% CIs will be plotted by study treatment.
	Categorical Change from Baseline to CCI and CCI in NYHA class	Categorical Change from Baseline in NYHA class will be one of the following nominal value: Worsened: post baseline NYHA class is larger than baseline NYHA class Unchanged: post baseline NYHA class is the same as baseline NYHA class Improved: post baseline NYHA class is smaller than baseline NYHA class	The number of subjects and corresponding percentage for worsened case, unchanged case and improved case will be summarized for CCI and CCI . The categorical change in New York Heart Association Class (improved, no change, or worsened) from baseline will be analyzed using a longitudinal proportional odds model. The response variable of the analysis model will be the change in NYHA class from baseline. The independent variables of the model will include the categorical effect of treatment, time, treatment-by-time interaction and the stratification factors, and baseline NYHA class as a covariate. Odds ratio and 95% CI relative to placebo will be reported for improved vs no change or worsened, and for improved or no change vs worsened. For missing NYHA change category data, the category worsened is assigned for death. For other reason of missingness, no imputation will be conducted.
To assess the effect of LY3540378 on patient-reported outcomes	Change from baseline through CCI of KCCQ: Total Symptom Score (TSS) Clinical Summary Score, and (CSS)	For each score, the change from baseline at each nominal visit is defined as: post baseline score – baseline score Detailed scoring instructions are provided in Appendix 7 (Section 6.7).	Same MMRM model as in Section 4.1 will be applied. LSM estimates with 95% CIs through CCI will be plotted by study treatment.

Objectives	Relative to the efficacy measure	Endpoint definition	Analysis conducted
	Overall Summary Score (OSS)		
	Change from baseline through CCI of CCI PGIS-HF Overall Health PGIS-HF Symptom Severity	For each PRO, the change from baseline at each nominal visit is defined as: post baseline score – baseline score	Same MMRM model as in Section 4.1 will be applied. LSM estimates with 95% CIs through CCI will be plotted by study treatment. Same MMRM model as in Section 4.1 will be applied. LSM estimates with 95% CIs through CCI will be plotted by study treatment.
	CCI	CCI at each visit	The Summary of number of subjects and percentage of subjects whose the CCI respectively in CCI and CCI

4.5.2. Clinical outcome events of Heart Failure

The following outcome events will be adjudicated by an independent clinical endpoint committee (CEC) external to Lilly to Lilly with cardiology expertise. CV death (CV and non-CV)

- Death: CV death and non-CV death
- hospitalization for heart failure (HF)
- urgent HF visits (urgent outpatient visits, unscheduled office, or emergency visit for HF)

This committee will be blinded to treatment assignment.

Only adjudicated outcome events will be considered as AESI. The counts and percentages of participants with adjudicated events may be summarized by treatment.

A listing of participants reporting the outcome events, either reported by investigator or identified by the CEC, will be provided. The listing will include treatment, participants identification including the site number, date of event, type of event as reported by the investigator, type of event as adjudicated by the CEC, time from first dose of study drug to the event, and time from last dose to the event (if participant has discontinued study drug prior to the event).

The counts and percentages of participants with the composite endpoint of CV death, hospitalization for HF or urgent HF visits will also be summarized by treatment. Kaplan-Meier plots of time to the composite event will be provided.

4.5.3. Outpatient Hemodynamic CV Medications

The endpoints related to outpatient hemodynamic CV medications are Change in the dosing of each of the following medications:

- diuretics (loop and thiazide)
- RAAS inhibitor
- SGLT-2i
- Beta blockers
- ARNI, and
- MRA.

Categorical change from baseline dose level will be one of the following nominal value: reduced, unchanged, increased. The number of subjects and corresponding percentage for reduced case, unchanged case and increased case will be summarized for each scheduled visit.

4.5.4. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic (PK), pharmacodynamic (PD), and PK/PD analysis are the responsibility of Lilly's PK/PD group.

LY3540378 concentration-time data will be summarized in the clinical study report.

Dose/exposure-response analyses between LY3540378 dose/concentration and key safety, tolerability, and efficacy points may be explored graphically or performed using population PK and population PK/PD approaches implemented in the Nonlinear Mixed Effects Modeling (NONMEM) software. Additionally, the impact of intrinsic and extrinsic factors (such as age, weight, sex, immunogenicity, renal, and hepatic functions) on PK and/or PD parameters may be evaluated where applicable.

4.5.5. Immunogenicity

At the visits and times specified in the protocol schedule of activities (Section 1.3 of the protocol), venous blood samples will be collected (if local regulations and ethical review boards allow) and stored for potential future analysis to determine antibody production against LY3540378. If the data is available at the time of final database lock, the following analysis will be conducted.

Treatment-emergent antidrug antibodies (TE ADAs) are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). A patient is evaluable for TE ADA if the patient has a nonmissing baseline ADA result, and at least 1nonmissing postbaseline ADA result.

Listings of patients who are not TE ADA evaluable, patients with at least one test having detected LY3437943 ADAs, and patients having LY3540378 ADAs present or TEAE: hypersensitivity reactions or injection site reactions will be provided.

The frequency and percentage of patients with preexisting ADA and with TE ADA will be tabulated by dose (if data warrant), where proportions are relative to the number of patients who are TE ADA evaluable. The frequency and percentage of patients with hypersensitivity and injection site reaction treatment-emergent adverse events (TEAEs) by TE ADA status will be tabulated if data warrant.

4.5.6. Bayesian Analyses for Dose-Response

4.5.6.1. Bayesian Analyses for Dose-Response at Week 12 and 26

For change from baseline in a key efficacy endpoint (e.g. LARS) at Week 26, we assume it satisfies a 3-parameter Emax model:

$$Y_i = E_0 + \frac{E_{max} d_i}{ED_{50} + d_i}$$

Here Y_i is the change from baseline at Week 26 for an efficacy endpoint of subject i, d_i is the dose level received by subject i, E_0 represent the basal effect when the dose level is 0 (placebo), E_{max} represents the maximum effect that can be achieved by any dose level on top of placebo, and ED_{50} is the dose level that produces half of the maximum effect.

The estimation of the parameters will be carried out in a Bayesian framework assuming noninformative priors for the hyperparameters in the model as follows:

$$\begin{cases} E_0 \sim N(0, 100^2), \\ E_{max} \sim N(0, 100^2), \\ ED_{50} \sim N^+(0,400), \end{cases}$$

where $N^+(0,400)$ is truncated normal distribution by bounding above 0. Posterior inference will be drawn for the dose-response at each dose level of LY3540378 and the 95% credible intervals will also be plotted.

The same Bayesian analysis will be applied for change from baseline at Week 12 for a key efficacy endpoint. Other dose-response model may also be explored if the above Emax model is not suitable.

4.5.6.2. Bayesian Analyses for Longitudinal Dose-Response

The longitudinal dose-response model as proposed by Fu and Manner (2010) will be applied here. Let d_{it} be the dose level taken by subject i at Week t , and Y_{it} be the change from baseline of an endpoint (e.g. LARS) for subject i at Week t. The model is as follows

$$Y_{it} = \beta_0 Baseline_i + f(t;k)(\lambda(d_{it}) + S_i) + \varepsilon_{it}.$$

Function $f(t;k)$ handles the time information and is assumed to be monotone with a pattern of exponential decay:

$$f(t;k) = \frac{1 - \exp(k_d t)}{1 - \exp(k_d T)}$$

where $T = 26$ is the maximum duration of the treatment period in weeks. Function $\lambda(d_{it})$ is the dose-response model for the maximum response at dose d, and assumed to be a 3-parameter Emax model:

$$\lambda(d) = \alpha_0 + \frac{\alpha_1 d}{\alpha_2 + d}$$

Here we use different parameters to distinct them from the Emax model in Section 4.5.6.1. In addition, δ_i is the between-subject random error term, ε_{it} is the within-subject random error term. We assume $S_i \sim N(0, \sigma_S^2)$ and $\varepsilon_{it} \sim N(0, \sigma^2)$ are independent.

The estimation of those parameters will be carried out in a Bayesian framework assuming noninformative priors for the hyperparameters in the model as follows:

$$\begin{cases} k_d \sim \text{uniform}(0,1), \\ \alpha_0 \sim N(0, 100^2), \\ \alpha_1 \sim N(0, 100^2), \\ \alpha_2 \sim N^+(0,400), \\ \frac{1}{\sigma_S^2} \sim Gamma(0.01,0.01), \\ \frac{1}{\sigma^2} \sim Gamma(0.01,0.01). \end{cases}$$

Posterior inference will be drawn for the dose-response at Week t of clinical interest and the 95% credible intervals will also be plotted.

4.6. Safety Analyses

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3540378 doses with placebo irrespective of adherence to study drug. Thus, safety analyses will be conducted using the safety analysis set.

4.6.1. Extent of Exposure

Listing of exposure to LY3540378 and placebo will be provided by treatment group using data from SS. Summary of duration of follow-up (defined as time in days from date of randomization to the date of the last study visit) and/or duration on study treatment (defined as time in days from date of first dose of study treatment to date of last dose of study treatment plus 7 days) will be provided by treatment group using data from SS, in the following period:

- 26 weeks plus safety follow-up (Visit 801 and 802) for all randomized participants.

For the summary of duration on study treatment, the frequency and percentage of participants falling into the following range will be summarized by planned treatment group as well:

In addition, the frequency and percentages of participants falling into the following study treatment exposure ranges may be summarized by planned treatment group:

CCI

No p-values will be reported in these summaries as they are intended to describe the study populations rather than test hypotheses about them.

*Temporary Discontinuation (TD) of Study Treatment*Number of subjects and percentage who had TD will be summarized by each treatment group. The number of doses which are not administered per protocol schedule of activities (Section 1.3 of the protocol) subject will also be summarized by treatment group, within those subjects who had TD.Subjects one the highest dose 100 mg are allowed to down titrate dose level to 50 mg. Number of subjects and percentage who had this down titration will be summarized by each treatment group. The number of doses which are down titrated per subject will also be summarized within those subjects who had dose down titration.

4.6.2. Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in severity after the first dose. The Medical Dictionary for Regulatory Activities (MedDRA) low level term (LLT) will be used in the treatment-emergent derivation. The maximum severity for each LLT during the baseline period including ongoing medical history will be used as baseline severity. Events with a missing baseline severity will be treated as "mild" in severity for determining treatment-emergence. Events with a missing severity during the postbaseline period will be treated as "severe" and treatment-emergence will be determined by comparing to baseline severity.

For events occurring on the day of first taking study medication, the case report form collected information (for example, treatment emergent flag, start time of study treatment and event) will be used to determine whether the event was pre- versus post-treatment if available. If the relevant information is not available, then the events will be counted as posttreatment.

The counts and percentages of participants with TEAEs will be summarized by treatment using MedDRA preferred terms (PTs) nested within system organ class (SOC). Comparisons will be applied at both the SOC and PT levels. Events will be ordered by decreasing frequency within SOC. The SOC will be in alphabetical order. For events that are sex-specific, the denominator and computation of the percentage will include only participants from the given sex.

An overview of the number and percentage of participants who experienced a TEAE, a serious adverse event (SAE), or death, discontinued from study treatment or study due to an AE, and relationship to study drug will be summarized by treatment.

The counts and percentages of patients with TEAEs by maximum severity will be summarized by treatment using MedDRA PT. For each participant and TEAE, the maximum severity for the MedDRA PT is the maximum postbaseline severity observed from all associated LLTs mapping to the MedDRA PT. The maximum severity will be determined based on the non-missing severities. If all severities are missing for the defined postbaseline period of interest, it will show as missing in the table.

4.6.2.1. AE of Special Interest (AESI)

The following are the AESIs:

- vaginal haemorrhage,
- breast tumors,
- hypotension,
- orthostatic hypotension,tissue changes in the female reproductive tracts, and
- anaemia.

The counts and percentages of patients with each category of AESIs by maximum severity will be summarized by treatment.

4.6.3. Patient Narratives

Patient narratives will be provided for all participants who experience any of the following "notable" events:

- death,
- serious AE,
- pregnancy, or
- permanent discontinuation of study treatment due to AEs.

Patient narratives (patient level data and summary paragraph) will be provided for participants in the randomized population with at least 1 notable event.

4.6.4. Vital Signs

In the case that multiple records of an individual vital sign are collected at the same visit, they will be averaged prior to being used for data summaries and analyses. For example, blood pressure (BP) and pulse rate (PR) are triplicated at Visit 2, 5, 6, 16, 18, 24 and early discontinuation per protocol schedule of activities (Section 1.3 of the protocol). The measurements will be averaged first.

Descriptive summaries by treatment and by nominal visit will be provided for baseline and postbaseline values as well as change from baseline values.

Treatment differences in mean change will be analyzed using the MMRM model as described in Section 4.1 for the safety analysis set.

Counts and percentages of participants with treatment-emergent abnormal supine systolic blood pressure (BP), diastolic BP, and pulse will be presented by treatment for participants who have both baseline and at least 1 postbaseline result:

- Treatment-emergent high result: a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any time that meets the specified change criteria during the postbaseline period.
- Treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time that meets the specified change criteria during the postbaseline period.

To assess decreases, change from the minimum value during the baseline period to the minimum value during the postbaseline period will be used. To assess increases, changes from the maximum value during the baseline period to the maximum value during the postbaseline period will be used. Both planned and unplanned measurements will be included in the analysis. The criteria for identifying patients with treatment-emergent vital sign abnormalities are stated in

Parameter	Low	High
Systolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤90 and decrease from baseline ≥20	≥129 and increase from baseline ≥20
Diastolic BP (mm Hg) (Supine or sitting – forearm at heart level)	≤50 and decrease from baseline ≥10	≥90 and increase from baseline ≥10
Pulse (bpm) (Supine or sitting)	<50 and decrease from baseline ≥15	>100 and increase from baseline ≥15

4.6.5. Clinical Laboratory Evaluation

All laboratory data will be reported in SI units. Selected laboratory measures will also be reported using conventional units. Limits from the performing lab will be used to define low (L) and high (H). Descriptive summaries by treatment and by nominal visit will be provided for the baseline and postbaseline values as well as the change from baseline values.

Observed and change from baseline values for each visit may be displayed in plots for participants who have both a baseline and at least 1 postbaseline planned measurement. Baseline will be the last non-missing observation prior to taking first study drug. Unplanned measurements will be excluded from plots.

A shift table will be provided including unplanned measurements. The shift table will include the number and percentage of participants within each baseline category (low, normal, high, or missing) versus each postbaseline category (low, normal, high, or missing) by treatment. The proportion of participants shifted will be compared between treatments using Fisher's exact test.

For qualitative laboratory analytes, the number and percentage of participants with normal and abnormal values will be summarized by treatment.

A listing of abnormal findings will be created for laboratory analyte measurements, including qualitative measures. The listing will include participant identification, treatment group, laboratory collection date, study day, analyte name, and analyte finding.

The MMRM model or ANCOVA (if MMRM model is not applicable) will be used for the analysis during the treatment period for the continuous measurements for selected lab tests.

4.6.6. Additional Safety Assessments

4.6.6.1. Hepatobiliary Disorders

The counts and percentages of participants with treatment-emergent potentially drug-related hepatobiliary disorders will be summarized by treatment using the PTs nested within Standardized MedDRA Queries (SMQs). Detailed search criteria can be found in Appendix 6 (Section 6.6).

4.6.6.1.1. Liver Enzymes

Analyses for laboratory analyte measurements are described in Section 4.6.5. This section describes additional analyses of liver enzymes.

Hepatic labs include alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL), direct bilirubin (DBL), serum alkaline phosphatase (ALP), international normalized ratio (INR), and gamma-glutamyl transferase (GGT). When criteria are met for hepatic evaluations, investigators will conduct close monitoring of hepatic symptoms and liver tests, perform a comprehensive evaluation for alternative causes of abnormal liver tests, and complete follow-up hepatic safety electronic case report form (eCRFs).

The following will be analyzed for hepatic safety (Table EZDB.4.5):

Table EZDB.4.5. Summary Tables and Figures Related to Hepatic Safety

Analysis	Population or Analysis Set
Abnormal Postbaseline Categories – Hepatic Safety Parameters ALT • The number and percentage of participants with a measurement greater than or equal to 1×, 3×, 5×, 10×, and 20× the performing lab ULN during the treatment period for all participants with a postbaseline value. AST • The number and percentage of participants with a measurement greater than or equal to 1×, 3×, 5×, 10×, and 20× the performing lab ULN during the treatment period for all participants with a postbaseline value. ALP • The number and percentage of participants with a measurement greater than or equal to 2× and 3× the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline. TBL • The number and percentage of participants with a measurement greater than or equal to 2×, 5×, and 8× the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value. DBL • The number and percentage of participants with a measurement greater than or equal to 2× and 5× the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value.	FAS

GGT • The number and percentage of participants with a measurement greater than or equal to 2× the performing lab ULN during the treatment period will be summarized for all participants with a postbaseline value.	
Hepatocellular Drug-Induced Liver Injury Screening Plot (TBL vs. ALT or AST)	FAS
Hepatocellular Drug-Induced Liver Injury Screening Table	FAS
Cholestatic Drug-Induced Liver Injury Screening Plot (TBL vs. ALP)	FAS
Cholestatic Drug-Induced Liver Injury Screening Table	FAS
Participant profiles will be created for participants meeting criteria for a comprehensive hepatic evaluation (as defined in the protocol). Participant profiles will include demographics, disposition, information collected on the hepatic safety CRFs (where applicable) and a display of study drug exposure, adverse events, medications, blood pressure, heart rate, and the liver-related measurements over time.	FAS

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRF = case report form; DBL = direct bilirubin; FAS = full analysis set; GGT = gamma-glutamyl transferase; TBL = total bilirubin; ULN = upper limit of normal.

Planned and unplanned measurements will be included. The measurements do not need to be taken at the same blood draw. Maximum baseline will be the maximum nonmissing observation in the baseline period. The maximum value will be the maximum nonmissing value from the postbaseline period. Planned and unplanned measurements will be included.

The primary purpose of the screening plots is to identify participants whose data warrant further review. For these plots, symbols will be used to indicate the randomized treatment.

For individual participants of interest, participant profiles will be reviewed. The review will include which treatment the participant was taking over time, the changes in hepatic labs over time, and the temporal association with potential causes. The review of participant profiles will also include the identification of any potential Hy's law case or potential cholestatic liver injury case that could have been missed by focusing only on the maximum values when determining 30-day time associations.

4.6.6.2. Hypersensitivity Events

Hypersensitivity reactions and related information reported in eCRF will be listed and summarized by treatment.

Summaries of all potential hypersensitivity reactions will be generated by PT with decreasing frequency by treatment. The AE database will be searched using predefined SMQs to identify events consistent with hypersensitivity events. Detailed search criteria can be found in Appendix 6 (Section 6.6).

4.6.6.3. Injection Site Reactions

Injection site reactions, incidence, and related information reported in eCRFs will be summarized by treatment. Information to be summarized includes the timing of the reaction relative to study drug administration, and characteristics of the injection site reaction: erythema, induration, pain, pruritus, and edema.

Additionally, potential injection site reactions will be searched by predefined MedDRA high level terms (HLTs) of injection site reactions, administration site reactions, and infusion-related reactions. Detailed searching criteria for injection site reaction events can be found in Appendix 6 (Section 6.6). The PT will be used for summary by treatment within each HLT category.

4.6.6.4. Renal Safety

Two shift tables examining renal function will be created:

- A min-to-min shift table of estimated glomerular filtration rate (eGFR) estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation with unit mL/min/1.73 m^2, using categories (<30, ≥30 to <45, ≥45 to <60, ≥60 to <90, and ≥90 mL/min/1.73 m^2), and
- Max-to-max shift table of urine albumin-to-creatinine ratio (UACR), using the categories UACR <30 g/kg, 30 g/kg ≤ UACR ≤300 g/kg, and UACR >300 g/kg (respectively, these represent normal, microalbuminuria, and macroalbuminuria).

The MMRM model will be used for the continuous measurements of the log-transformed UACR. Refer to Section 4.1 and Table EZDB.4.1 for analysis details of variables which needs log-transformation.

4.6.6.5. Major Adverse Cardiovascular Events (MACE)

In addition to the clinical outcome event of HF (Section 4.5.2), the following nonfatal cardiovascular AEs (NCAE) will also be adjudicated by CEC:

- myocardial infarction
- hospitalization for unstable angina
- coronary interventions, such as coronary artery bypass graft or percutaneous coronary intervention, and
- cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

The counts and percentages of participants with adjudicated NCAE may be summarized by treatment.

In addition, NCAE reported by investigator may also be summarized although an NCAE reported by investigator is not considered as AESI.

A listing of participants reporting NCAE events, either reported by investigators or identified by the aforementioned committee, will be provided. The listing will include treatment, participants' identification, including the site number, date of event, type of event as reported by the

investigator, type of event as adjudicated by the physician committee, time from first dose of study drug to the event, and time from last dose to the event (if participant has discontinued study drug prior to the event).

4.7. Other Analyses

4.7.1. Subgroup Analyses

Subgroup analyses of the following primary endpoint and secondary endpoints will be made to assess consistency of the intervention effect:

- LARS
- log-transformed NT-proBNP
- LAEDVI
- LAESVI, and
- eGFR

Where the subgroups are defined as follows:

- age: < median vs ≥ median
- sex: female versus male
- race: white, Asian, others
- baseline NYHA class: I-II vs III-IV
- region: North America, Latin America, Asia, Europe and other countries
- atrial fibrillation or atrial flutter on the screening ECG: Yes vs. No
- baseline value of the endpoint: < median vs ≥ median

For each subgroup analysis, the following 2 models will be conducted:

- MMRM model as described in Section 4.1 on the subgroup only.
- Full MMRM model: the MMRM model as described in Section 4.1 adding interactions between subgroup and visit, between subgroup and treatment and between subgroup, treatment and visit as fixed effects.

If the number of participants is too small (less than 10%) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study.

For safety lab variable hemoglobin, subgroup analysis will be done for each sex group (female vs. male) using MMRM model described in Section 4.1.

Additional subgroup analyses may also be performed.

4.8. Interim Analyses

There may be up to 4 interim analyses including primary database lock.

A planned interim analysis may be conducted when between 40% and 80% of the participants complete Week 26 at CCI or discontinue the study. The interim will be for the purpose of internal planning and decision-making and may assess safety, PK, and/or efficacy measures. At the discretion of the sponsor, the prespecified interim analysis may not be conducted. If

prespecified interim analysis happens, an AC will be formed to review the interim analyses in an unblinded manner. The details regarding the number of participants and type of analysis will be provided in the AC charter and in the unblinding plan. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team members before the study has been unblinded. Study sites will receive information about interim results only if deemed necessary for the safety of the participants. The study will not be stopped based on the efficacy of LY3540378 versus placebo. Therefore, there will be no inflation of the type 1 error rate, and no need to employ an alpha spending function or multiplicity adjustment.

The primary database lock and primary data analysis for Study EZDB may occur when all participants have completed 26 weeks CCI of treatment. The final database lock and final data analysis will occur when all randomized participants have completed the study. Participants and investigators will remain blinded until the completion of the study. If there is no primary database lock, the primary analysis will be based on the final database lock.

Early access to the PK and PD data before the interim and primary database locks may be conducted to allow population PK/PD analysis and model development. If applicable, this early access will be detailed in the Unblinding Plan and the Population PK/PD Analysis Plan.

5. Sample Size Determination

The sample size calculation is based on the primary efficacy estimand and its endpoint, change from baseline at Week 26 in LARS.

For participants who joined study before amendment (b), they were randomized 1:1:1:1 to the following intervention groups:

- LY3540378 25 mg SC QW
- LY3540378 50 mg SC QW
- LY3540378 100 mg SC QW, and
- placebo.

For participants who joined study after amendment (b), will be randomized 1:2:2:2 to the above intervention groups.

Up to 456 participants will be randomly assigned to ensure at least 114 participants enrolled in each of 50 mg, 100 mg, and placebo groups. Assuming a 20% dropout rate, this will result in at least 91 completers in each of 50 mg, 100 mg, and placebo group. The number of completers in 25 mg will be approximately 64 to 91, depending on when the amendment (b) is globally implemented.

The evaluation of superiority to placebo will be conducted for LY3540378 doses of 50 and 100 mg and combination of 50 and 100 mg. No adjustment for multiplicity will be performed. Assuming a standard deviation of 8.5%, and a 2-sided, alpha level of 0.05, 91 completers for each treatment arms will provide 88% power to detect a treatment difference of 4% for the primary endpoint for LY3540378 50 mg group versus placebo and LY3540378 100 mg group versus placebo, respectively.

6. Supporting Documentation

6.1. Appendix 1: Demographic and Baseline Characteristics

A listing of participant demographics for all randomized participants will be provided. All demographic and baseline clinical characteristics will be summarized by treatment groups for all randomized participants.

Baseline demographic and clinical characteristics of special interest include but are not limited to:

- demographics: age (years), sex (female, male), race, ethnicity, height (cm), weight (kg), BMI (kg/m^2),
- baseline HF status: NYHA class, atrial fibrillation or flatter at screening
- disease history: history of atrial fibrillation, hypertension, diabetes, myocardial infarction, anemia
- baseline of selected ECHO parameters: LARS, LAEDVI, LAESVI, LA emptying fraction, LVGLS, E/A, E/e', LVM, LVMI,
- Baseline of selected lab data: NT-proBNP,BNP, BNP, eGFR (creatine- CKD-EPI, mL/min/1.73m^2), eGFR groups (<30, ≥30 to <45, ≥45 to <60, ≥60 to <90, and ≥90 mL/min/1.73 m^2), serum creatine, cystatin-C, UACR, UACR groups of normal(<30) microalbuminuria (≥30 to <300) and macroalbuminuria (≥300), high sensitivity troponin (hs-cTnT)
- Baseline vital Signs: supine systolic and diastolic blood pressure in supine position
- Baseline heart rate
- Baseline treatments: diuretics, RAAS inhibitor, SGLT-2i, Beta blockers, ARNI, and MRA

6.2. Appendix 2: Historical Illnesses and Pre-existing Conditions

The count and percentages of participants with historical illnesses and preexisting conditions will be summarized by treatment groups using the MedDRA PTs nested within SOC. The SOC will be in alphabetical order. Conditions (that is, PTs) will be ordered by decreasing frequency within SOC. This will be summarized for all randomized participants.

6.3. Appendix 3: Treatment Compliance

Listing and summary of prematurely discontinuing study treatment (including discontinuation reason) and discontinuing study will be provided by treatment groups.

If data warrants, the counts and percentages of participants who have dose interruption or have dose de-escalation will be summarized for each treatment group.

Overall treatment compliance will be defined as taking at least 75% of the scheduled LY3540378 or placebo doses. Compliance will be calculated by taking the number of doses administered (regardless of the actual dose in mg administered) divided by the total number of doses expected to be administered, and then multiplied by 100. Overall treatment compliance will be summarized descriptively by treatment group using the full analysis set.

6.4. Appendix 4: Concomitant Medications

Concomitant medications will be summarized by treatment group. The percentages of participants who took concomitant medication will be summarized by treatment using PTs nested within Anatomical Therapeutic Chemical (ATC) Level 3 codes. The concomitant medications will be ordered by decreasing frequency within each ATC level.

6.5. Appendix 5: Important Protocol Deviations

Important protocol deviations are identified in the Trial Issues Management Plan. A listing and summary of important protocol deviations by treatment groups will be provided at the end of study (for all randomized participants).

6.6. Appendix 6: Searching Criteria for Additional Safety Assessments

Hepatic treatment-emergent adverse events

Treatment-emergent, potentially drug-related hepatic disorders will be summarized by treatment using the MedDRA PTs contained in any of the following SMQs:

- Broad and narrow terms in the Liver related investigations, signs and symptoms SMQ (20000008)
- Broad and narrow terms in the Cholestasis and jaundice of hepatic origin SMQ (20000009)
- Broad and narrow terms in the Hepatitis non-infections SMQ (20000010)
- Broad and narrow terms in the Hepatic failure, fibrosis and cirrhosis and other liver damage SMQ (20000013)
- Narrow terms in the Liver-related coagulation and bleeding disturbances SMQ (20000015)
- Narrow PTs in Gallbladder related disorders SMQ (20000124)
- Narrow PTs in Biliary tract disorders SMQ (20000125), and
- Narrow PTs in Gallstone related disorders SMQ (20000127).

Injection site reactions

Treatment emergent injection site reaction will be summarized by treatment using the MedDRA PT in any of the following MedDRA HLTs:

- Injection site reaction
- Administration site reaction, and
- Infusion site reactions.

Vaginal haemorrhage

Vaginal haemorrhage will be summarized by treatment using the MedDRA PT in any of the following MedDRA HLTs:

- Reproductive system haemorrhages
- Vulvovaginal disorders NEC

Breast Tumours

Breast Tumours will be summarized by treatment in any of the following MedDRA HLTs:

- Breast and nipple neoplasms benign
- Breast neoplasms unspecified malignancy
- Breast and nipple neoplasms malignant

Hypotension

Hypotension will be summarized by treatment using the MedDRA PT in MedDRA HLT Vascular hypotensive disorders.

Orthostatic Hypotension

Orthostatic Hypotension will be summarized by treatment the MedDRA PT in any of the following MedDRA HLTs:

- Vascular hypotensive disorders
- Autonomic nervous system disorders

Tissue Changes in the Female Reproductive Tracts

Orthostatic Hypotension will be summarized by treatment in any of the following MedDRA HLTs:

- Cervix neoplasms benign
- Ovarian neoplasms benign
- Reproductive neoplasms female benign NEC

Anaemia

Anaemia will be summarized by treatment using the MedDRA PT in MedDRA HLT Anaemias NEC.

6.7. Appendix 7: The Kansas City Cardiomyopathy Questionnaire Scoring Instructions

1. Physical Limitation

Code responses to each of Questions 1a-f as follows:

- Extremely limited = 1
- Quite a bit limited = 2
- Moderately limited = 3
- Slightly limited = 4
- Not at all limited = 5
- Limited for other reasons or did not do = <*missing value*>

If at least three of Questions 1a-f are not missing, then compute

Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) – 1]/4

Note: If there are n questions in a scale, and the subject must answer m to score the scale, but the subject answers only n-i, where n-i >= m, calculate the mean of those questions as

(sum of the responses to those n-i questions) / (n-i)

not

(sum of the responses to those n-i questions) / n

2. Symptom Stability

Code the response to Question 2 as follows:

- Much worse = 1
- Slightly worse = 2
- Not changed = 3
- Slightly better = 4
- Much better = 5
- I've had no symptoms over the last 2 weeks = 3

If Question 2 is not missing, then compute

$$\text{Symptom Stability Score} = 100*[(\text{Question 2}) - 1]/4$$

3. Symptom Frequency

Code responses to Questions 3, 5, 7 and 9 as follows:

Question 3

- Every morning = 1
- 3 or more times a week but not every day = 2
- 1-2 times a week = 3
- Less than once a week = 4
- Never over the past 2 weeks = 5

Questions 5 and 7

- All of the time = 1
- Several times a day = 2
- At least once a day = 3
- 3 or more times a week but not every day = 4
- 1-2 times a week = 5
- Less than once a week = 6
- Never over the past 2 weeks = 7

Question 9

- Every night = 1
- 3 or more times a week but not every day = 2
- 1-2 times a week = 3
- Less than once a week = 4

- Never over the past 2 weeks = 5

If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

S3 = [(Question 3) – 1]/4

S5 = [(Question 5) – 1]/6

S7 = [(Question 7) – 1]/6

S9 = [(Question 9) – 1]/4

Symptom Frequency Score = 100*(mean of S3, S5, S7 and S9)

4. Symptom Burden

Code responses to each of Questions 4, 6 and 8 as follows:

- Extremely bothersome = 1
- Quite a bit bothersome = 2
- Moderately bothersome = 3
- Slightly bothersome = 4
- Not at all bothersome = 5
- I've had no swelling/fatigue/shortness of breath = 5

If at least one of Questions 4, 6 and 8 is not missing, then compute

Symptom Burden Score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

5. Total Symptom Score

Total Symptom Score = mean of the following available summary scores:

- Symptom Frequency Score
- Symptom Burden Score

6. Self-Efficacy

Code responses to Questions 10 and 11 as follows:

Question 10

- Not at all sure = 1
- Not very sure = 2
- Somewhat sure = 3
- Mostly sure = 4
- Completely sure = 5

Question 11

- Do not understand at all = 1
- Do not understand very well = 2
- Somewhat understand = 3
- Mostly understand = 4
- Completely understand = 5

If at least one of Questions 10 and 11 is not missing, then compute

Self-Efficacy Score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4

7. Quality of Life

Code responses to Questions 12, 13 and 14 as follows:

Question 12

- It has extremely limited my enjoyment of life = 1
- It has limited my enjoyment of life quite a bit = 2
- It has moderately limited my enjoyment of life = 3
- It has slightly limited my enjoyment of life = 4
- It has not limited my enjoyment of life at all = 5

Question 13

- Not at all satisfied = 1
- Mostly dissatisfied = 2
- Somewhat satisfied = 3
- Mostly satisfied = 4
- Completely satisfied = 5

Question 14

- I felt that way all of the time = 1
- I felt that way most of the time = 2
- I occasionally felt that way = 3
- I rarely felt that way = 4
- I never felt that way = 5

If at least one of Questions 12, 13 and 14 is not missing, then compute

Quality of Life Score = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

8. Social Limitation

Code responses to each of Questions 15a-d as follows:

- Severely limited = 1
- Limited quite a bit = 2
- Moderately limited = 3
- Slightly limited = 4
- Did not limit at all = 5

Does not apply or did not do for other reasons = <*missing value*>

If at least two of Questions 15a-d are not missing, then compute

Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

9. Overall Summary Score

Overall Summary Score = mean of the following available summary scores:

- Physical Limitation Score
- Total Symptom Score
- Quality of Life Score
- Social Limitation Score

10. Clinical Summary Score

Clinical Summary Score = mean of the following available summary scores:

- Physical Limitation Score
- Total Symptom Score

7. References

Fu H, Manner D. Bayesian adaptive dose-finding studies with delayed responses. *J Biopharm Stat*. 2010;20(5):1055-1070. https://doi.org/10.1080/10543400903315740

Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. *N Engl J Med*. 2021;385(19):1737-1749. https://doi.org/10.1056/NEJMoa2102953

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