DOCUMENT: Statistical Analysis Plan

PROTOCOL: SNFCT2015-05

A double-blind, randomised, placebo-controlled study to assess the effect of SNF472 on progression of cardiovascular calcification on top of standard of care in end-stage-renal-disease (ESRD) patients on haemodialysis (HD)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (SGPT)
ANCOVA	analysis of covariance
AST	aspartate transaminase (SGOT)
ATC	Anatomical Therapeutic Chemical
AU	Agatston units
BMD	bone mineral density
BMI	body mass index
BUN	blood urea nitrogen
CAC	coronary artery calcium
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CV	cardiovascular
CVC	cardiovascular calcification
DBP	diastolic blood pressure
DEXA	dual-energy x-ray absorptiometry
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
E/e' ratio	ratio of mitral inflow early diastolic to mitral annular velocity
ESRD	end-stage renal disease
ET	early termination
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HD	hemodialysis
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IMP	investigational medicinal product
INR	international normalized ratio
ITT	Intent-to-treat
IV	intravenous
LA	left atrial
LDH	lactic acid dehydrogenase
LM	left main coronary artery

Abbreviation	Definition
LOCF	last observation carried forward
LS	least square
LV	left ventricular
LVMI	left ventricular mass index
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
min	minimum
mL	milliliter
MMRM	mixed model repeated measures
mITT	Modified intent-to-treat
NCI	National Cancer Institute
PE	physical examination
PP	per protocol
PT	prothrombin time
PTH	parathyroid hormone
PTT	partial thromboplastin time
PWV	pulse wave velocity
QTc	corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse events
TESAE	treatment-emergent serious adverse events
TSAT	transferrin saturation
WBC	white blood cell
WHO	World Health Organization

1 INTRODUCTION

This document describes the statistical methods and data presentations, summaries and analyses of the safety, tolerability, and efficacy data from the clinical protocol SNFCT2015-05 amendment 5.0 to be displayed and contained within the main body of the CSR. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and electronic case report forms (eCRFs) for details of study conduct and data collection. Additional analyses are included within this SAP to address particular clinical issues. A separate SAP or addendum to this SAP will be written to provide the statistical methods, presentations and analyses for the protocol sub-study, pharmacokinetics, pharmacodynamics, and biomarkers.

2 STUDY OBJECTIVE(S), TREATMENTS, AND ENDPOINT(S)

2.1 Main Study Objectives

2.1.1 Main Study Primary Objective

The primary objective of the main study is to assess the effect of 2 dose levels of SNF472 (300 mg and 600 mg) compared to placebo on the progression of coronary artery calcium (CAC) volume score over a 12-month (52 weeks) period in ESRD subjects on HD.

2.1.2 Main Study Secondary Objectives

The secondary objectives of the main study are to:

- assess change from baseline* (Week 1, Day 1) in CAC/Agatston score
- assess the number of subjects with <15% progression in CAC/Agatston score
- assess the number of subjects with >15% progression in CAC volume scores
- assess the change from baseline* in thoracic aorta calcification score
- assess the change from baseline* in aortic valve calcification score
- assess the occurrence of the composite safety endpoint: death from cardiovascular (CV) causes, myocardial infarction (MI), stroke, or heart failure
- assess changes in biomarkers as signals for treatment efficacy/response
- assess changes in bone mineral density (BMD)
- describe the long-term safety profile of SNF472 in the target population

*All references to baseline CAC/Agatston scores or other calcification scores are the screening visit scores.

2.1.3 Main Study Exploratory Objectives

The exploratory objective of the main study is to assess changes from baseline in pulse pressure, systolic blood pressure (SBP), and diastolic blood pressure (DBP).

2.2 Sub-Study Objectives

The Sub-Study objectives will be described in a separate SAP that will, when available, form an addendum to the main SAP.

2.3 Treatment Groups

This study is a multicenter, double-blind, randomized, placebo-controlled, phase 2b study. Subjects will be randomized to either one of two active drug dose levels or placebo (1:1:1).

All subjects will receive 2 identical vials of 10 mL:

- Placebo arm: 2 vials of physiological saline
- Dose 1 arm (300 mg): 1 vial of physiological saline and 1 vial of active (10 mL SNF472 at 30 mg/mL)
- Dose 2 arm (600 mg): 2 vials of active (10 mL SNF472 at 30 mg/mL).

2.4 Main Study Endpoints

2.4.1 Main Study Primary Endpoints

The main study primary endpoint is the change in log CAC volume scores between baseline (Week 1, Day 1) and Week 52 for the combined dose groups vs placebo as measured by computed tomography (CT).

2.4.2 Main Study Secondary Endpoints

The main study secondary endpoints are:

- change in log CAC volume score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo
- change from baseline in log CAC/Agatston score at Week 52 for combined dose groups, and each dose group (300mg and 600 mg) vs placebo
- number of subjects with <15% progression in CAC/Agatston score at Week 52 for combined dose groups, and each dose group (300mg and 600 mg) vs placebo
- number of subjects with >15% progression in CAC volume score at Week 52 for combined dose groups, and each dose group (300mg and 600 mg) vs placebo
- change from baseline in log thoracic aorta calcification (Volume and Agatston score) at Week 52 for combined dose groups, and each dose group (300mg and 600 mg) vs placebo
- change from baseline in log aortic valve calcification (Volume and Agatston score) at Week 52 for combined dose groups, and each dose group (300mg and 600 mg) vs placebo
- incidence of composite safety endpoint that include death from cardiovascular causes, MI, stroke, or heart failure
- mortality rate (all-cause and CV)
- change from baseline in levels of selected biomarkers, analysis and presentation of these data will be described in a separate SAP or an addendum to this main SAP.
- changes in log BMD levels between baseline and Week 52
- safety of SNF472 in terms of incidences of adverse events (AE) and serious adverse events (SAE) and QTc, and clinically relevant changes from baseline in laboratory and electrocardiogram (ECG) parameters.

2.4.3 Main Study Exploratory Endpoints

The main study exploratory endpoints are changes from baseline in pulse pressure, SBP, and DBP at Week 28 and Week 52 in all subjects by treatment arm, combined dose (300mg and 600 mg) and overall.

2.6 Safety Evaluations

One of the main study secondary objectives is to describe the long-term safety profile of SNF472 in the target population. This will be accomplished by evaluation of changes in BMD levels between baseline and Week 52 and in terms of incidences of adverse events (AE) and serious adverse events (SAE) and clinically relevant changes from baseline in laboratory and electrocardiogram (ECG) parameters.

An AE is defined by the International Council for Harmonization (ICH) Guideline for Good Clinical Practice (ICH E6 GCP) as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.

The National Cancer Institute (NCI) Common Terminology Criteria (CTCAE) version 4.03 will be used to grade AEs.

A serious adverse event (SAE) is an event that results in any of the following:

- Death
- Life-threatening situation (subject is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity (substantial disruption of the ability to carry out normal life functions)
- Congenital anomaly or birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in this definition.

HD-related AEs will be recorded throughout the duration of study drug infusion in the eCRF.

All AEs will be monitored and recorded starting from the date of the first administration of the study drug through the subject's early termination (Early Termination (ET) visit) or until scheduled completion (Week 52 visit). All SAEs will be monitored and recorded starting from the first study drug administration until Week 56 (or 30 days after last administration of study drug).

Other safety evaluations will include:

- Hematology measures: hematocrit, hemoglobin, platelet count, white blood cell (WBC) count (total and differential)
- Chemistry measures: alanine transaminase (ALT), albumin, alkaline phosphatase (ALP), amylase, aspartate transaminase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, gamma-glutamyl transpeptidase (GGT), glucose, lactic acid dehydrogenase (LDH), magnesium, potassium, sodium, total bilirubin, total protein, uric acid, phosphorus
- Coagulation measures: international normalized ratio (INR), partial thromboplastin time (PTT), prothrombin time (PT)
- Parathyroid hormone (PTH), transferrin saturation (TSAT), ferritin
- Pregnancy Test
- Vital Signs: heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, temperature
- Physical Examination (PE), weight, and height
- QTc

- 12-Lead ECG (normal, abnormal- not clinically significant, abnormal- clinically significant).

Outcomes of the combined dose groups may also be analyzed for secondary, exploratory and safety endpoints not described here as post-hoc analyses.

3 STUDY DESIGN

3.1 Main Study Design

This study is designed as multicenter, double-blind, randomized, placebo-controlled, phase 2b study to evaluate the effects of 2 dose levels of SNF472 on progression of cardiovascular calcification (CVC) as measured by CAC volume scores and CAC scores (Agatston) in ESRD subjects on HD. The randomization will be stratified by baseline CAC score category. Subjects will be randomized to either one of two active drug dose levels or placebo (1:1:1). Approximately 75 sites in 3 countries will enroll approximately 270 subjects. The study will consist of a screening period, a 52-week double-blind treatment period, and a follow-up visit. See Section 3.3 for the main study summary of scheduled assessments. The study treatment duration of 52 weeks has been selected as an appropriate duration likely to provide clinically meaningful changes in the primary outcome. It is expected that N=190/270 subjects will provide Week 52 data. A non-binding futility analysis is planned when approximately 119/270 subjects have provided Week 52 data.

Screening is scheduled 28 + 3 days prior to randomization. Rescreening will be performed on a case-by-case basis after discussion with the Medical Monitor.

In the treatment period, a single intravenous (IV) dose of one of two dose levels of SNF472 (300 mg or 600 mg) or placebo (randomized 1:1:1) will be delivered in conjunction with each HD session (3 times weekly) over 52 weeks. CT scans will be done at baseline and Week 52 to determine CAC scores. A follow-up visit will be performed at Week 56 or one month (30 days) after last dose of study drug, for assessment of SAEs only.

A Data and Safety Monitoring Board (DSMB) will monitor subject safety and data integrity. Please refer to the DSMB Charter for details on the roles and responsibilities of the DSMB.

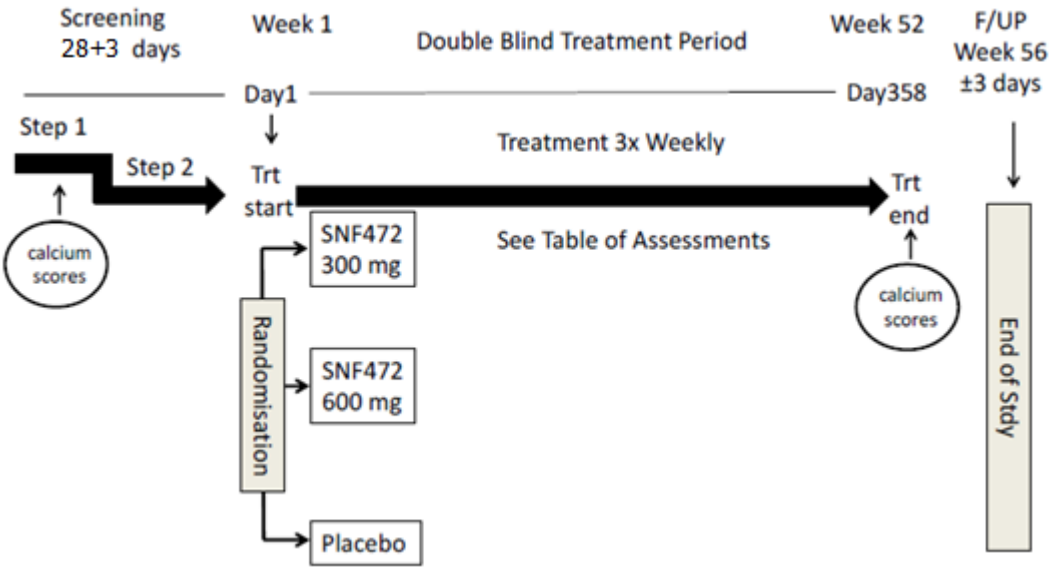
All subjects who discontinue prematurely will continue with their standard of care dialysis sessions. They will report for an ET visit. Sites will make every effort to get post-baseline CT scans and dual-energy x-ray absorptiometry (DEXA) and to have subjects return for a follow-up visit.

Subjects withdrawn from the study will not be replaced.

CT images of the thoracic area (chest) will be collected and reviewed by [redacted] to determine the CAC/Agatston score, CAC volume score, thoracic aorta calcification (Volume and Agatston score) and the aortic valve calcification (Volume and Agatston score) at Screening (considered to be baseline) and Week 52/ET. DEXA images of the hip will be collected and reviewed by [redacted] to assess BMD (total hip and femoral neck) changes from Screening (considered the baseline BMD) and Week 52/ET. The same imaging equipment, method of assessment and scanning techniques will be used throughout the course of the study at each imaging center to ensure consistency during the study.

A study flowchart is provided in Figure 1 below.

Figure 1. Study Flowchart



3.3 Main Study Summary of Scheduled Assessments

Table 1. Main Study Schedule of Assessments

Procedures	Screening[a] 28 + 3 days		Double Blind Treatment Period											Wk 56 or 1 month after last dose
			156 VISITS: Study Drug Infusion Administered at Each HD Session (3x Weekly)[k]											
	Key Evaluation Visits (Preferably at Mid-Week Dialysis Sessions)													
Week	Step 1[a]	Step 2[a]	Wk 1	Wk 2	Wk 4	Wk 6	Wk 10	Wk 16	Wk 22	Wk 28	Wk 34	Wk 40	Wk 46	Wk 52/ET[m]	
Day			1	8 (±3 d)	22 (±3 d)	36 (±3 d)	64 (±3 d)	106 (±3 d)	148 (±3 d)	190 (±3 d)	232 (±3 d)	274 (±3 d)	316 (±3 d)	358 (±3 d)	
Informed consent[b]	X														
Eligibility, inclusion/exclusion criteria[c]	X	X	X												
CT scan for calcium scores for screening[d] and endpoints	X													X	
DEXA for BMD[e]	X													X	
Evaluation of CT scan at Step 1 must be completed before proceeding to Step 2															
Medical history, demographics		X													
Physical exam, including height and weight		X												X	

Procedures	Screening[a] 28 + 3 days		Double Blind Treatment Period											Wk 56 or 1 month after last dose
			156 VISITS: Study Drug Infusion Administered at Each HD Session (3x Weekly)[k]											
	Key Evaluation Visits (Preferably at Mid-Week Dialysis Sessions)													
Week	Step 1[a]	Step 2[a]	Wk 1	Wk 2	Wk 4	Wk 6	Wk 10	Wk 16	Wk 22	Wk 28	Wk 34	Wk 40	Wk 46	Wk 52/ET[m]	
Day			1	8 (±3 d)	22 (±3 d)	36 (±3 d)	64 (±3 d)	106 (±3 d)	148 (±3 d)	190 (±3 d)	232 (±3 d)	274 (±3 d)	316 (±3 d)	358 (±3 d)	
Treatment history, current and prior medication		X													
Pregnancy[f]		X	X			X	X	X	X	X	X	X	X	X	
12-lead ECG (including QTc)[g]		X					X			X		X		X	
Vital signs[h]		X	X	X		X		X		X		X		X	
Randomisation			X												
Haematology, coagulation, and chemistry[i]			X				X			X		X		X	
PTH, TSAT, ferritin			X											X	
Plasma PK sampling[j]			X				X		X					X	
Biomarkers sampling[j]			X				X		X					X	
Blinded study drug infusion (3x weekly)[k]			X	X	X	X	X	X	X	X	X	X	X	X	
Post-dialysis weight			X				X			X		X		X	
Change in concomitant medications[l]			X		X		X			X				X	
AE assessment			X	X	X	X	X	X	X	X	X	X	X	X	X (SAEs only)

AE: adverse event; BL: Baseline; BMD: bone mineral density; CAC: coronary artery calcium; CT: computed tomography; DEXA: dual-energy x-ray absorptiometry; ECG: electrocardiogram; ET: early termination; PK: pharmacokinetic(s); PTH: parathyroid hormone; SAEs: serious adverse events; TSAT: transferrin saturation; Wk: week

[a] Screening will proceed in 2 steps: Step 1 will involve informed consent followed by the CT scan for CAC score and BMD by DEXA for Screening. Only those patients who are eligible in Step1 can proceed to Step 2.

[b] Patients will provide written informed consent before any clinical study-specific procedures are performed.

[c] The inclusion/exclusion criteria will be assessed for each patient at Screening and will be confirmed again on Day 1 prior to randomisation.

[d] CT scan of coronary artery using a multi-detector CT with at least 64 slices to quantify calcium scores for Step 1 screening. Only patients who meet the inclusion criterion of CAC score of 100 to 3500 AU (Agatston Units) will proceed to Screening Step 2.

[e] BMD will be measured by DEXA at the same visits at the CT scan.

[f] For females of child-bearing potential, serum pregnancy test.

[g] ECG will be performed at Screening and **post-dialysis** at the visits indicated.

[h] Vital signs include heart rate, respiratory rate, blood pressure and body temperature **post-dialysis**. These are recorded for the study at key visits only. Standard of care vital signs assessments are not being recorded into study database at each HD visit.

[i] Blood samples will be collected **pre-dose** via the dialysis port for haematology, coagulation, and chemistry tests.

[j] Only for patients at participating sites, the PK and biomarker samples will be collected via the dialysis port at **pre-dose and at 3 hrs (~10 minutes before end of infusion)** on the assessment day. Biomarkers may include but are not limited to fetuin A, FGF23, MGP, sclerostin, pharmacodynamics (PD), and GDF15. **No genetic testing will be performed**.

[k] The treatment period is 52 weeks, and study treatment is administered at each HD session (3x weekly following the standard procedure established by the nephrologist). Intravenous doses of either SNF472 or matching placebo will be administered to patients in conjunction with each HD session (see Section 5.5). **Except for Baseline (Day 1), intensive data collection visits are recommended to be done on the 2nd dialysis session of each week (mid-week HD session).**

[l] Record change in concomitant medications relative to previous assessment visit; only prescription medications are to be recorded.

[m] The early termination (ET) visit will replace the Week 52 visit if the patient terminated the study earlier than planned. PK and biomarker samples will be collected during this visit if the post-baseline samples haven't been collected prior to early termination. A CT scan for calcium quantification and BMD by DEXA should be done. If not feasible for this visit, the site must make all efforts to set an appointment for a CT scan and DEXA. In addition, sites must encourage patients to report for the follow-up visit.

4 SAMPLE SIZE CONSIDERATIONS

4.1 Main Study Sample Size Considerations

The hypothesized values for CAC volume score (Agatston) at baseline and Week 52 for placebo (standard-of-care) are provided in Table 2 below. These data are derived from the ADVANCE trial (Raggi 2010). The standard deviation (SD) of the change from baseline to Week 52 in calcium volume scores is estimated to be 0.30 on the log scale (Raggi 2010).

Table 2 Hypothesized values for calcium volume score at baseline and Week 52 for placebo

	Placebo
Assumed percentage change in calcium volume score progression from baseline to Week 52	35%
Expected raw calcium volume score at Week 52 assuming a raw calcium volume score of 380 at baseline (Week 1, Day 1)	513
Expected change in log-transformed calcium volume score progression from baseline to Week 52	0.30
Estimated standard deviation of change in log-transformed calcium volume scores from baseline to Week 52	0.30

It is planned to randomize N=270 subjects (i.e., 90 per group) with N=190 expected to provide Week 52 data in the final analysis. A non-binding interim analysis for futility is planned when N=119 subjects (63% of N=190) have provided Week 52 data. The purpose of this interim is ascertain if the conditional power for achieving a statistically significant result in the final analysis on the high dose plus low dose combined vs. placebo would be low, ≤ 5%; if so the study may be declared futile and subject follow-up may consequently cease. There is no plan or intent to curtail follow-up at this interim for a positive efficacy finding.

Assuming a 35% progression in CAC score on placebo at Week 52, and allowing for the futility interim analysis, this trial has 80% overall power with an overall 1-sided alpha level of 2.44% to test the hypothesis that the true difference between SNF472 high dose vs placebo in log CAC progression scores is 0.150. This corresponds to a true ratio of CAC progression scores, SNF472 high dose vs placebo, of 1.162 which, in turn, corresponds to a 16.2% progression score on SNF472 high dose vs 35% on placebo.

The corresponding value for the average of the two SNF472 doses vs placebo to provide 80% overall power to test the hypothesis that the true difference between SNF472 average dose vs placebo alone in log CAC progression scores is 0.130. This corresponds to a true ratio of CAC progression scores, SNF472 average dose vs placebo of 1.139 which, in turn, corresponds to a 18.5% progression score on SNF472 average dose vs 35% on placebo.

5 ANALYSIS POPULATIONS

5.1 Enrolled Population

The enrolled population is defined as all subjects who have signed the informed consent, are not screen failures, and who are randomized. The enrolled population will be used for disposition tables.

5.2 Modified Intent-to-Treat (mITT) Population

The main-study mITT population will consist of all randomized subjects, who receive at least one dose of study drug, and have at least one evaluable post-baseline scan (Either Week 52 or ET). An evaluable scan is defined as a scan with a non-missing CAC volume score.

Subjects will be analyzed according to the treatment to which they were randomized. The mITT population will be the primary efficacy analysis population.

5.3 Per Protocol (PP) Population

The main-study per protocol population is a subset of the mITT population who:

- met all inclusion/exclusion criteria
- have an evaluable baseline scan and completed the study including a Week 52 dosing visit and have a Week 52 evaluable follow-up scan (the Week 52 scan could have been done up to 120 days after last dose of study drug). An evaluable scan is defined as a scan with a non-missing CAC volume score.
- have at least 80% exposure to study drug (as determined by the number of doses actually administered vs the total number of doses anticipated over the baseline to Week 52 study period)

The main-study PP population will be used as the secondary/supportive efficacy analysis population.

5.4 Safety Population

The Safety population will consist of all randomized subjects who receive at least one dose of study drug. Subjects will be analyzed according to the treatment they received*. The Safety population will be used for analyses of AEs and safety endpoints.

*The majority of the treatment dose group, or placebo that the subject received throughout the subject's full participation will determine the treatment group for analysis.

6 CONSIDERATIONS FOR DATA ANALYSIS

6.1 Programming Environment

All analyses will be conducted using SAS® version 9.3 or above.

6.2 Strata and Covariates

The primary efficacy analysis will be adjusted for log CAC volume score at the screening evaluation as a covariate. The analysis will be stratified by the CAC Agatston score 100-399, 400-1000 and >1000 measured at the screening evaluation and assigned at randomization

As an exploratory analysis, the following clinically relevant baseline covariates will be included in the primary analysis model: sex, age, race, dialysis vintage, and diabetes. In addition, a secondary analysis model will include sex, age, race, dialysis vintage, diabetes, PTH, magnesium (Mg), non-calcium phosphate binders, statins, warfarin, Activated Vitamin D and arteriosclerotic cardiovascular disease (ASCVD).

6.3 Subgroups

The primary endpoint will be examined in the following baseline subgroups to assess the consistency of the overall main study result:

- Age
- Sex
- Diabetes
- Dialysis Vintage (< 2yrs, >=2 to < 5yrs, > 5 yrs)
- ASCVD
- Non-calcium phosphate binders
- Statins
- Calcimimetics
- Activated Vitamin D
- Warfarin
- Calcium-based phosphate binders

For each subgroup, the main study analysis model will be re-run with additional terms for subgroup and subgroups by randomized treatment interaction so that the LS means for each treatment group (including combined group) and treatment effects can be extracted and presented for each level of the subgroup.

Refer to Appendix 1 for descriptions or definitions of subgroups as applicable.

6.4 Multiple Comparisons and Multiplicity

There are no planned adjustments for multiple hypothesis testing.

6.5 Significance Level

Unless otherwise specified, all statistical analyses will be conducted using a two-sided significance level (α) of 0.05 and two-sided hypothesis testing.

6.6 Statistical Notation and Methodology

Unless stated otherwise, the term “descriptive statistics” refers to the number of subjects (n), mean, median, SD, minimum (min), and maximum (max) for continuous data and frequencies (counts and percentages) for categorical data. Min and max values will be rounded to the precision of the original value, means and medians will be rounded to 1 decimal place greater than the precision of the original value, and SDs will be rounded to 2 decimal places greater than the precision of the original value. Percentages will be rounded to the nearest whole number (zeros will not be displayed), with values of “<1%” and “>99%” shown as necessary for percentages falling near the boundaries. If data is recorded as “<x.xx” or “>x.xx” for analysis this will be converted to “x.xx”, for categorical data it will be presented as recorded. P-values will be presented with 4 decimal places of precision.

Unless otherwise noted, all data collected during the study will be included in subject data listings and will be sorted by study site, subject ID, treatment group, and date/time within each subject.

6.7 Randomization

Randomization will be used to avoid bias and to enhance the validity of statistical comparisons. Blinded treatment (active and matched placebo) will be used to reduce potential bias during data collection and evaluation of clinical endpoints.
Randomization should occur on Day 1 after all pre-dose procedures have been performed and eligibility for the clinical trial has been confirmed. However, it is acceptable for the first dose to occur on a later day than randomization to accommodate for pharmacy/ study drug preparation needs. For clarity, Day 1 Week 1 is the first dose date. Randomization will be performed using a centralized electronic randomization system.

Due to the strong association of baseline CAC/Agatston score with subsequent calcification progression, baseline CAC/Agatston score will be used as a randomization stratification factor by breaking into three categories (100-399, 400-1000 and >1000). In keeping with the ICH E9 guidance, baseline CAC/Agatston score will be included in the primary efficacy analysis.

6.8 Visit Windows

In the summary and analysis of data by visit, all data will be grouped by nominal visit as shown in Table 3:

Table 3. Visit Windows Used for Summary of Data

Scheduled Visit Week	Target Study Day	Visit Window (Days)
Screening	-28	-31 to ≤0
Week 1	1	>0 to ≤5
Week 2	8	>5 to ≤15
Week 4	22	>15 to ≤29
Week 6	36	>29 to ≤50
Week 10	64	>50 to ≤85
Week 16	106	>85 to ≤127
Week 22	148	>127 to ≤169
Week 28	190	>169 to ≤211
Week 34	232	>211 to ≤253
Week 40	274	>253 to ≤295
Week 46	316	>295 to ≤337
Week 52	358	>337 to ≤478

If more than one value falls within the assigned visit window, the mean of those values will be taken and used for summarization. Visit windows are intended to be contiguous such that all data collected at all post-baseline visits, whether scheduled or unscheduled, will map to one of the visits. The visit displayed on subject data listings will show both the scheduled visit as reported on the eCRF and the assigned visit as per Table 1. Study days relative to baseline will be displayed for each visit.

7 DATA HANDLING METHODS

7.1 Missing Values

7.1.1 Date Values

The missing component(s) of incomplete dates (e.g. start and/or stop dates of AE, concomitant medication, medical history, years since primary ESRD diagnosis) will be assumed as the most conservative value possible. For example, if the start date has a missing day value, the first day of the month will be imputed for study day computations. If day is missing for an end date, the last day of the month will be imputed. Similar logic will be assumed for missing month and year components. If the years since primary ESRD diagnosis is fully missing, a date of 6 months prior to signing the informed consent will be used. This is consistent with the protocol requirement at entry.

For determination of treatment-emergent status, the start date will be imputed as the date of the first dose of study drug. AEs will be considered treatment-emergent if all or part of the date of onset of the AE is missing and it cannot be determined if the AE meets the definition for treatment-emergent.

Date imputation will only be used for computational purposes such as treatment-emergent status. Actual date values, as they appear in the original eCRFs, will be presented in the subject data listings. All dates that will be imputed in the analyses will be indicated with an asterisk (*) in the data listing.

7.1.2 Analysis Values

The primary efficacy analysis will impute missing Week 52 calcification scores which include CAC volume score, CAC/Agatston scores, thoracic aorta volume and Agatston scores and aortic valve volume and Agatston scores via last observation carried forward (LOCF) imputation of the Early termination visits.

Per the Summary to Scheduled Events Table 1, subjects who discontinue early will have a CAC assessment at the time of discontinuation – for those subjects, that last CAC volume score will be used for the missing Week 52. However, if a subject has only a screening CAC volume score, the Week 52 value will remain missing.

In addition to LOCF imputation, additional analyses using multiple imputation will be implemented to explore the impact of missing data. As above if a subject only has a screening CAC volume score, no imputation will be performed.

Firstly, missing data will be imputed within each arm using distribution implied by the non-missing subject data for that arm. Secondly, missing data will be imputed for all arms using distribution implied by the non-missing subject data within the placebo arm. Further, tipping point analyses may be performed to assess how extreme a departure in the distribution of data from subjects with missing values would have to be to render the primary endpoint analysis non-significant.

7.2 Data Derivations

Baseline values will be considered as the last non-missing assessment prior to the first administration of study drug.

Unless otherwise specified, change from baseline calculations for a treatment window assessment will be the applicable treatment window assessment minus the baseline assessment (i.e., change from baseline [CFB] = treatment window assessment – baseline).

For a given date within the treatment window, Study Day will be computed as the given date minus Day 1 date plus 1 day (i.e., Study Day = Date – Day 1 + 1). For a given date within the screening window, Study Day will be computed as the given date minus Day 1 plus 1 day (i.e., Study Day = Date – Day 1 + 1).
A treatment-emergent AE (TEAE) is defined as an AE that begins or that worsens in severity after the first dose of the study drug through the subject's early termination (Early Termination (ET) visit) or until scheduled completion (Week 52 visit).

Dialysis vintage (days) will be defined as screening visit step 2 date – hemodialysis start date (01MMMYYYY) + 1. Note that this start date is recorded as MMMYYYY on the demographics eCRF, so it will be assumed to start on the first day of the month.

Medications will be defined as prior or concomitant. Prior medications include medications taken prior to the first dose of study drug. At Screening, the subject's medication use history of the past 30 days will be recorded in the eCRF. Changes in prior medications through the Screening period will be documented prior to the first dose of study drug. Concomitant medications include all medications taken with or after the first dose of study drug. Only prescription medications will be recorded.

8 STUDY POPULATION

8.1 Subject Enrollment and Disposition

The following summary will be generated for All Screened Subjects:

1. Enrollment and disposition data will be summarized by treatment group and overall as the number of subjects screened, the number and percentage (n, %) of subjects: with screening failures and primary reason subjects failed entry into the study, enrolled, who were randomized but not treated, who had stent placement after infusion, who completed the study, and who discontinued from the study. In addition, the number and percentage of subjects within each study discontinuation reason category will be presented by treatment group and overall.

The following summary will be generated for All Enrolled Subjects (Enrolled subjects are those who are randomized) Subjects will be analyzed according to the treatment to which they were randomized.

1. Analysis population summary will be provided as the number and percentage (n, %) of subjects in each analysis population (main-study mITT, main-study PP and safety) by treatment group and overall.

The following listings will be generated:

1. Enrollment information will be provided in a data listing by subject. It will include information on whether the subject belongs in the following populations: main-study mITT, main-study PP and safety.
2. Discontinuation information will also be provided in a data listing.

8.2 Protocol Deviations

The number and percentage (n, %) of subjects with at least one deviation, with at least one major deviation, and the number and percentage of subjects within each major and minor deviation category will be summarized by treatment group and overall. Summaries will be provided for clinical deviations from the protocol and analysis deviations from the protocol.

All protocol deviations will be reviewed prior to unblinding and classified as either major or minor. Protocol deviation categories include but are not limited to:

- Inclusion/exclusion criteria
- Protocol required evaluation not completed
- Non-compliance with study drug administration
- Other

Major protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

All protocol deviations (both major and minor) will be provided in a data listing and tabulated by deviation type versus randomized treatment arm.

8.3 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria deviations will be provided in a data listing.

8.4 Demographic and Baseline Characteristics Assessment

Subject demographics at screening: age, sex (if female, specify if subject has child bearing potential), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, and Unknown), and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and Not Reported), will be summarized by treatment group and overall for the mITT, PP, and Safety populations. Sex, ethnicity, and race will be summarized as the number and percentage (n, %) of subjects within each category. Age will be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, min, and max).

Weight and height will be assessed at screening. Height will be defined as baseline if it is recorded prior to or up to 1 week after treatment start date (≤ study day 5). Baseline body mass index (BMI) will be computed as (weight in kilogram) / (height in meters)^2. BMI will be summarized as a continuous variable using descriptive statistics (n, mean, SD, median, min, and max).

In addition, SBP and DBP at baseline will also be summarized using descriptive statistics (n, mean, SD, median, min, and max).

Separate summary tables will be provided for subjects: (1) in the main study safety population, (2) in the mITT population, and (3) in the PP population

Demographic and baseline characteristics will also be summarized by DEXA and CT status as follows for the safety population:

1. Subjects with Baseline and Week 52 DEXA(/CT) Scan

2. Subjects with Baseline and ET DEXA(/CT) Scan
3. Subjects with Baseline DEXA(/CT) Scan only

Demographic and baseline characteristics data will be provided in a data listing.

8.5 Disease Characteristics

Disease characteristics at baseline will be summarized with descriptive statistics by treatment group and overall. These include CAC/Agatston score stratification categories (100-399, 400-1000, and >1000) at randomization, CAC/Agatston score at randomization, years since primary ESRD diagnosis, and dialysis vintage.

Dialysis vintage in months is defined as [(screening step 2 date - hemodialysis start date) + 1] / 30. Note that hemodialysis start date is recorded as MMMYYYY on the eCRF, so it will be assumed to start on the first day of the month.

Separate summary tables will be provided for subjects: (1) in the main study safety population, and (2) in the mITT population.

Disease Characteristics will also be summarized by DEXA and CT status as follows for the safety population:

1. Subjects with Baseline and Week 52 DEXA(/CT) Scan
2. Subjects with Baseline and ET DEXA(/CT) Scan
3. Subjects with Baseline DEXA(/CT) Scan only

Disease characteristics will be provided in a data listing by subject.

8.6 Prior and Concomitant Medications

Medication usage will be coded using the World Health Organization (WHO) Drug Dictionary.
Medication use will be presented for the mITT and Safety populations by WHO Drug Anatomical/Therapeutic/Chemical (ATC) category and WHO Drug preferred name.
Summaries will be provided by treatment group and overall. Medications with partial start and/or stop dates, which cannot be definitely categorized as prior or concomitant will be considered concomitant.
The following medications will be summarized, and detailed preferred terms provided: statins, warfarin, sevelamer, calcium-based phosphate binders, calcimimetics, non-calcium-based phosphate binders, lanthanum, either sevelamer or lanthanum, iron-based phosphate binders, and activated vitamin D.

Specific prior medications will also be summarized by DEXA and CT status as follows for the safety population:

1. Subjects with Baseline and Week 52 DEXA(/CT) Scan
2. Subjects with Baseline and ET DEXA(/CT) Scan
3. Subjects with Baseline DEXA(/CT) Scan only

Prior and concomitant medications will be provided in a data listing.

8.6 Selected Laboratory Measures

Summaries will be provided by treatment group and overall. Magnesium and intact parathyroid hormone (PTH) will be summarized. These parameters will also be summarized by DEXA and CT status as follows for the safety population:

1. Subjects with Baseline and Week 52 DEXA(/CT) Scan
2. Subjects with Baseline and ET DEXA(/CT) Scan
3. Subjects with Baseline DEXA(/CT) Scan only

Selected laboratory measures will be provided in a data listing.

8.7 Medical Procedures Completed During the Study

Medical procedures completed during the study will be provided in a data listing.

8.8 Medical History

Medical history data will be provided in a data listing and summarized by randomized treatment arm in the following categories diabetes mellitus, hypertension, peripheral vascular disease, cerebrovascular accident, myocardial infarction, coronary artery disease, and congestive heart failure.

9 EFFICACY ANALYSIS

9.1 Main Study Efficacy Analysis

All primary and secondary efficacy endpoints will be analyzed using the mITT population and PP populations. As described below, sensitivity analyses will be performed to examine the impact of missing data on the primary efficacy analysis.

All baseline assessments will be based on the last assessment performed prior to the administration of the first dosing of study drug.

All efficacy will be performed on the adjusted baseline data, aside from the stratification CAC Agatston score categories which will be based on original baseline data.

CAC volume scores, CAC/Agatston scores, and aortic valve and thoracic aorta calcification (volume and Agatston scores) and change from baseline to Week 52/ET (LOCF) will be summarized by visit, treatment group (300mg, 600mg, placebo and combined dose), and overall using descriptive statistics (mean, median, SD, min, max, Geometric mean, log (standard deviation), and number of subjects).

Comprehensive data listings will also be provided.

9.1.1 Main Study – Analysis for Primary Efficacy Endpoint

The main study primary endpoint is the change in log CAC volume scores between baseline (Week 1, Day 1) and Week 52 as measured by computed tomography (CT). The primary contrast of interest is that of the combined dose groups vs the placebo group.

The primary efficacy analysis will impute missing Week 52 CAC volume score using LOCF (see section 7.1.2) and will be done on the mITT population. The PP population will be used as the supportive analysis population.

For analysis, CAC Volume Score is defined as follows:

CAC Volume score (mm^3) = LM [Volume (mm^3)] + LAD-LCX-RCA[Volume (mm^3)];

Where LM is left main coronary artery and LAD-LCX-RCA represents the sum of left anterior descending coronary artery, the left circumflex coronary artery and the right coronary artery and their respective branches. Variable LAD-LCX-RCA, CAC Volume is a single value of the sum of the three arteries due to the data management requirements of the analysis software system as described in the Imaging Charter and the Data Transfer Specifications for this trial. If either LM or LAD-LCX-RCA are NE volume score will still be computed using the evaluable result.

CAC volume score values will be log-transformed prior to analysis. The primary analysis will use an ANCOVA model with the change in log volume score (log 52-week volume score – log baseline volume score) as the dependent variable and with a fixed effect term for randomized treatment group and log CAC volume score at baseline as a covariate; the model will also be stratified by the randomization stratification factor, i.e. screening CAC/Agatston score category.

Least square (LS) means for each of the treatment groups will be estimated and back transformed prior to presentation. The primary contrast of interest to assess treatment effect will be the combined dose vs placebo; supportive contrasts will be the difference in LS means between each dose and placebo. These contrasts and their estimated 95% confidence interval (CI) will be back transformed prior to presentation. P-value for each contrast will also be provided.

To facilitate data interpretation, the preceding ANCOVA will be re-run but with the log of the 52-week CAC volume as the dependent variable (i.e., without subtracting log baseline volume score). This will allow estimation of the absolute 52-week volume score by back transformation as well as the common baseline volume score so that the degree of absolute change in CAC volume score can be assessed in a fashion that is consistent with the preceding analysis of the change in log volume score.

9.1.2 Main Study – Analysis for Secondary Endpoints

The following secondary endpoints will be analyzed:

a) change in log CAC volume score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo
b) Change from baseline in log CAC/Agatston score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and for combined dose groups vs the placebo group
c) Number of subjects with <15% progression in CAC/Agatston score at Week 52 for each dose group, and combined dose group vs the placebo group
d) Number of subjects with >15% progression in CAC volume at Week 52 for each dose group and combined dose group vs the placebo group
e) change from baseline in log thoracic aorta calcification (volume and Agatston scores) at Week 52 for each dose group (300 mg and 600 mg) vs placebo and for combined dose group vs the placebo group
f) change from baseline in log aortic valve calcification (volume and Agatston scores) at Week 52 for each dose group (300 mg and 600 mg) vs placebo and for combined dose group vs the placebo group

g) incidence of composite safety endpoint that include death from cardiovascular causes, MI, stroke, or heart failure for each dose group and placebo
h) mortality rate (all-cause and CV) for each dose group, and placebo

Endpoints a), b) and e) and f) will be analyzed in the manner described in Section 9.1.1. Endpoint c) and d) will be analyzed in a manner detailed later in this section.

Endpoints g) and h) will be summarized in terms of number of events by randomized treatment arm. The time to the first of CV death, non-fatal MI, non-fatal stroke heart failure in endpoint g) will be analyzed using Cox proportional hazards modelling with a fixed effect term for randomized treatment group and log CAC volume score at baseline as a covariate; the model will also be stratified by the randomization stratification factor, i.e. screening CAC/Agatston score category. Subjects free from an event at their last study visit will be censored. The hazard ratio for the combined group vs placebo and for each dose vs placebo will be extracted from the analysis, along with the associated 95% CIs and p-values. The data will also be displayed in terms of a Kaplan-Meier plot.

The time to death from any cause, i.e. endpoint h), will be analyzed in the same manner as endpoint g)

For analysis, CAC Agatston score will be computed as follows:

CAC Agatston Score = LM –[Agatston] + LAD-LCX-RCA – [Agatston];

Where LM is left main coronary artery and LAD-LCX-RCA represents the sum of left anterior descending coronary artery, the left circumflex coronary artery and the right coronary artery and their respective branches. Variable LAD-LCX-RCA, CAC Agatston Score is a single value of the sum of the three arteries due to the data management requirements of the analysis software system as described in the Imaging Charter and the Data Transfer Specifications for this trial. If either LM or LAD-LCX-RCA are NE, Agatston score will still be computed using the evaluable result.

The aortic valve calcification Agatston score (AV) will include the aortic valve leaflets and aortic annular tissue. Calcium within the aortic sinus or on the aortic wall will be excluded from and not be measured as part of the aortic valve calcification Agatston score. Calcium outside of the aortic valve leaflets and aortic annulus will be included in the thoracic aortic calcification Agatston score described below.

The thoracic aortic calcification Agatston score will include the following segments:

- Aortic sinuses of valsalva
- Ascending thoracic aorta
- Transverse arch excluding the great vessels of the head and neck
- Descending thoracic aorta

The aortic valve calcification volume score will include the aortic valve leaflets and aortic annular tissue. Calcium within the aortic sinus or on the aortic wall will be excluded from and not be measured as part of the aortic valve calcification volume score. Calcium outside of the aortic valve leaflets and aortic annulus will be included in the thoracic aortic calcification volume score described below.

The thoracic aortic calcification volume score will include the following segments:

- Aortic sinuses of valsalva
- Ascending thoracic aorta

- Transverse arch excluding the great vessels of the head and neck
- Descending thoracic aorta

The secondary efficacy analyses will also impute missing Week 52 scores using LOCF unless otherwise stated. All secondary analyses will be done using the mITT population as the primary efficacy population and the PP population as the supportive analysis population.

If thoracic aorta volume/Agatston scores or aortic valve volume/Agatston scores are recorded as zero, they cannot be log transformed. Therefore, zero values will be imputed with the next smallest value in the relevant treatment arm for the secondary efficacy analysis. Results will be presented as recorded and as imputed in the data listings.

The proportion of subjects with < 15% progression in CAC/Agatston Score and >15% CAC volume from baseline to Week 52 will be summarized using descriptive statistics and analyzed using exact logistic regression. Progression is defined as an increase in score from baseline. The model will include a fixed effect term for randomized treatment group and log CAC volume score at baseline as a covariate; the model will also be stratified by the randomization stratification factor, i.e. screening CAC/Agatston score category. The exact odds ratio for the combined group vs placebo and for each dose vs placebo will be extracted from the analysis, along with the associated 95% CIs and p-values.

9.1.3 Main Study – Analysis for Exploratory Efficacy Endpoints

The exploratory efficacy variables are changes from baseline in pulse pressure, SBP, and DBP at Week 28 and Week 52. Pulse pressure will be computed as SBP – DBP. All exploratory efficacy analyses will be done using the mITT population as the primary efficacy population.

Pulse pressure, SBP, and DBP assessments and change from baseline to Week 28 and Week 52 will be summarized by visit, treatment group (300mg, 600mg, Placebo and Combined dose), and overall using descriptive statistics (mean, median, SD, min, max, and number of subjects).

Change from baseline in pulse pressure will be analyzed using a mixed-model for repeated measures (MMRM). The model will include baseline pulse pressure as covariate; screening CAC/Agatston score category, randomized treatment group, timepoint, and treatment group-by-time point interaction as fixed effects; subject will be included as a random effect. An unstructured covariance structure will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom.

Estimated LS means with the corresponding 2-sided 95% CI will be reported for pulse pressure change from baseline at Week 28 and Week 52. LS mean difference (95% CI) between the treatment groups (and combined group) will also be presented at each time point as well as p-values.

Similar analysis will be done for SBP and DBP.

9.1.4 Main Study Additional Efficacy Analysis

In addition to the primary efficacy analysis (which uses LOCF to account for missing data), additional analyses will be implemented to explore the impact of missing data and to assess the impact of covariates in the primary efficacy model.

9.1.4.1 Change in log CAC volume scores from baseline to Week 52 (LOCF) including Additional Covariates

As described in section 6.2, the primary efficacy analysis will be re-run including clinically relevant covariates in the analysis model.

If values for the laboratory parameters PTH and Magnesium are missing at baseline and therefore they cannot be utilized in the analysis, the values will be imputed with the mean value calculated across all relevant data obtained at baseline.

9.1.4.2 Change in log CAC volume scores from baseline to Week 52 (Multiple Imputation I)

Missing Week 52 CAC volume score will be imputed using SAS procedure MI within each treatment group and the combined dose groups using distribution implied by the non-missing subject data for that treatment group. This will be done for all missing week 52 CAC volume scores including for subjects who discontinued early. SAS code similar to the following will be used to impute missing values under the missing at random (MAR) assumption:

```
PROC MI data = <dataset _name>  SEED = <seed> NIMPUTE = 20 out = MI_Out;
        BY Treatment Arm;
        CLASS  Strata;
        MONOTONE REG ( logWeek52 = TreatmentArm Strata logBaseline );
        VAR  Strata logBaseline logWeek52;
RUN;
```

Post imputation, each imputed dataset will be analyzed separately using ANCOVA method similar to the primary efficacy analysis (see Section 9.1.1). SAS code similar to the following will be used:

```
DATA CFB_Out;   SET MI_Out;   logCFB = logWeek52 - logBaseline;   RUN;

PROC GLM DATA = CFB_Out;
        CLASS TreatmentArm Strata;
        MODEL logCFB =  TreatmentArm Strata logBaseline/ SOLUTION;
        ESTIMATE 'TreatmentArm 1 vs 3' TreatmentArm 1 -0 -1;
        ESTIMATE 'TreatmentArm 2 vs 3' TreatmentArm 0 1 -1;
        ESTIMATE 'TreatmentArm 1 and 2 vs 3' TreatmentArm 0.5 0.5 -1;
        BY  _Imputation_;
        ODS OUTPUT ESTIMATES = glm_est;
RUN;
```

The SAS procedure MIANALYZE will be used to combine the 20 sets of estimates by Rubin's rules. SAS code similar to the following will be used:

```
DATA glm_est (DROP=parameter1);
        SET glm_est(RENAME = (parameter= parameter1));
        parameter = COMPRESS(parameter1);
RUN;

PROC MIANALYZE PARMS = glm_est;
        MODELEFFECTS TreatmentArm1vs3 TreatmentArm2vs3 TreatmentArm1and2vs3;
RUN;
```

LS means for each of the 3 treatment groups and combined dose group will be estimated and back transformed prior to presentation. The main contrasts of interest to assess treatment effect will be the difference in LS means between each dose and placebo and between the average of the two doses vs placebo. These contrasts and their estimated 95% confidence interval (CI) will be back transformed prior to presentation. P-value for each contrast will also be provided.

The same analysis will be done for CAC/Agatston scores, thoracic aorta volume and Agatston scores and aortic valve volume and Agatston scores.

CAC volume/Agatston scores, thoracic aorta volume/Agatston scores and aortic valve volume/Agatston scores will have a minimum imputed value of 0 i.e. log(1).

9.1.4.3 Change in log CAC volume scores from baseline to Week 52 (Multiple Imputation II)

Missing Week 52 CAC volume score will be imputed using SAS procedure MI for all treatment groups and combined dose group using the distribution implied by the non-missing subject data within the placebo group. This will be done for all missing week 52 CAC volume scores including for subjects who discontinued early SAS code similar to the following will be used to impute missing values under the missing not at random (MNAR) assumption:

```
PROC MI data = <dataset _name>  SEED = <seed> NIMPUTE = 20 out = MI_Out;
        CLASS TreatmentArm Strata;
        MONOTONE REG ( / details);
        MNAR MODEL ( logWeek52 / MODELOBS = (TreatmentArm='3' ) );
        VAR Strata logBaseline logWeek52;
RUN;
```

Post imputation, each imputed dataset will be analyzed separately using ANCOVA method similar to the primary efficacy analysis (see Section 9.1.1). The 20 sets of estimates will then be combined by Rubin's rules using SAS procedure MIANALYZE. SAS code similar to the codes presented in Section 9.1.4.2 will be used.

LS means for each of the 3 treatment groups and the combined dose groups will be estimated and back transformed prior to presentation. The main contrasts of interest to assess treatment effect will be the difference in LS means between each dose and placebo and between the average of the two doses vs placebo. These contrasts and their estimated 95% confidence interval (CI) will be back transformed prior to presentation. P-value for each contrast will also be provided.

The same analysis will be done for CAC/Agatston scores, thoracic aorta volume and Agatston scores and aortic valve volume and Agatston scores.

CAC volume/Agatston scores, thoracic aorta volume/Agatston scores and aortic valve volume/Agatston scores will have a minimum imputed value of 0 i.e. log(1).

9.1.4.4 Change in log CAC volume scores from baseline to Week 52 (Tipping Point Analysis)

A tipping point analysis may be performed to assess how extreme a departure in the distribution of data from subjects with missing values would have to be to render the primary endpoint analysis non-significant.

The following SAS code will generate 20 imputed data sets for a specified shift parameter. The imputed values for subject data in the treatment arm specified will be adjusted using the shift parameter.

```
PROC MI data = <dataset _name>  SEED = <seed> NIMPUTE = 20 out = MI_Out;
        CLASS TreatmentArm Strata;
        MONOTONE REG ( logWeek52 = TreatmentArm Strata logBaseline);
        MNAR ADJUST ( logWeek52 / SHIFT = <shift>
                ADJUSTOBS = (TreatmentArm='<treatment>'));
        VAR TreatmentArm Strata logBaseline logWeek52;
RUN;
```

Post imputation, each imputed dataset will be analyzed separately using ANCOVA method similar to the primary efficacy analysis (see Section 9.1.1). The 20 sets of estimates will then be combined by Rubin's rules using SAS procedure MIANALYZE. SAS code similar to the codes presented in Section 9.1.4.2 will be used.

The process outlined above will be repeated for different shift values until a tipping point at which the study conclusions are overturned is found.

The same analysis will be done for CAC/Agatston scores, thoracic aorta volume and Agatston scores and aortic valve volume and Agatston scores.

CAC volume/Agatston scores, thoracic aorta volume/Agatston scores and aortic valve volume/Agatston scores will have a minimum imputed value of 0 i.e. log(1).

9.1.4.5 Sensitivity analysis for subjects with stent placement on study

Subjects may have stents placed whilst on the study. Placement of a stent during the treatment period could potentially influence the measurement of the coronary artery calcification at the follow-up visit. The core imaging lab recorded the observation of placement of a stent during the treatment period which may interfere with scoring of calcification and may lead to exclusion of some calcium quantification in sections of the image. The sensitivity analysis will be performed to assess the potential impact that these subjects on the primary and secondary efficacy endpoints a) b and d). Subjects who meet the criteria for stent placement will be removed from the analysis and the remaining subjects will be analyzed using the original analysis model; these subjects will also be listed separately. A list of subjects to be excluded due to stent placement will be provided by the core imaging lab

10 SAFETY ANALYSIS

All safety analyses will be performed on the safety population. Baseline values will be results from last assessment done prior to study drug administration.

10.1 Adverse Events

AEs will be classified into a standardized terminology using the Medical Dictionary for Regulatory Activities (MedDRA, version 19.1 or higher) system organ classifications and preferred terms. AEs will be assessed for severity. The National Cancer Institute (NCI) Common Terminology Criteria (CTCAE), version 4.03, for toxicity grade will be used to assign the severity for all AEs.

TEAEs are defined as AEs with an onset date on or after the date of first dose of study drug through 30 days after the last dose of study drug. This will include the subject's early termination (Early Termination

(ET) visit) or the scheduled completion (Week 52 visit). AEs will be considered treatment-emergent if all or part of the date of onset of the AE is missing and it cannot be determined if the AE meets the definition for treatment-emergent. This presentation of TEAE is consistent with the follow-up period designated in the protocol for TESAE.

TESAEs are defined as SAE with an onset date on or after the first dose of study drug until Week 56 and not to exceed 30 days after last dose of study drug.

All summaries of TEAEs will be provided using the Safety Population by treatment group and will be categorized by system organ class (SOC) and preferred term. These summaries will present the number and percentage of subjects reporting an AE for each classification level. Although a preferred term or system organ class may be reported more than once for a subject, each subject will only be counted once in the incidence count for that preferred term or system organ class.

The following summaries will be provided:

- TEAEs by MedDRA SOC and preferred term
- TEAEs by MedDRA SOC and preferred term, and Severity
- At Least Possibly Related TEAEs by MedDRA SOC and preferred term
- TEAEs Leading to Study Discontinuation by MedDRA SOC and preferred term
- TEAEs Leading to Study drug Withdrawal by MedDRA SOC and preferred term
- Grade ≥3 TEAEs by MedDRA SOC and preferred term
- Treatment-Emergent Serious Adverse Events (TESAEs) by MedDRA SOC and preferred term
- TESAEs by MedDRA SOC and preferred term, and Severity
- At Least Possibly -Related TESAEs by MedDRA SOC and preferred term
- TESAEs Leading to Study Discontinuation by MedDRA SOC and preferred term
- TESAEs Leading to Study drug Withdrawal by MedDRA SOC and preferred term
- Grade ≥3 TESAEs by MedDRA SOC and preferred term
- Death

During the course of this trial, AEs that did not begin within the temporal definition of TEAE may have been recorded in the database. These AEs will be presented in a separate data listing.

A separate listing will be included for TEAEs leading to discontinuation from study.

10.2 Mortality

All-cause mortality rate is defined as the percentage of subjects who have died during the study regardless of the cause of death. CV mortality rate is defined as the percentage of subjects who have died during the study due to CV causes. A summary of all-cause and CV mortality rate will be presented as the number and percentage of subjects in each category by treatment group and overall.

As described in Section 9.1.2, time to death (all-cause mortality) will be presented using Kaplan-Meier displays and analyzed using Cox regression. Kaplan-Meier's will be provided for all cause death, CV death and non-CV death. CV death is defined as any subject who is identified as part of the SCE (see appendix 1) and whom has a fatal outcome.

10.3 Incidence of Composite Safety Endpoint

As described in Section 9.1.2, the composite safety endpoint of time to the first of CV death, non-fatal MI, non -fatal stroke, or heart failure will be analyzed using Kaplan-Meier displays and analyzed using Cox regression.

Refer to Appendix 1 for descriptions or definitions as applicable.

10.4 Bone Mineral Density (BMD)

Change from baseline to Week 52/ET (LOCF) total hip BMD assessments and femoral neck BMD assessments will be summarized by visit, treatment group, and overall using descriptive statistics (mean, median, SD, min, max, and number of subjects).

Total hip and femoral neck BMD data will be displayed in a data listing by subject. Total hip and femoral neck BMD will be analyzed using the same analysis method as the primary efficacy model.

10.5 Hemodialysis Events

The number of hemodialysis (HD) events will be summarized by subject i.e. the number of subjects reporting 0, 1, 2, 3,… HD events will be determined and summarized by randomized treatment. HD events include chest pain, disequilibrium syndrome, fever and chills, headache, hypertension, hypotension, itching, muscle cramps, nausea and vomiting, and pyrogen reaction.

Time to the first HD event will be analyzed using the same Kaplan Meier and Cox regression methodology as described in Sections 9.1.2, 10.2 and 10.3.

10.6 Laboratory Evaluations (Hematology, Serum Chemistry, Coagulation, and Urinalysis)

Hematology laboratory evaluations include hematocrit, hemoglobin, platelet count, white blood cell (WBC) count (total and differential).

Serum chemistry laboratory evaluations include alanine transaminase (ALT), albumin, alkaline phosphatase (ALP), amylase, aspartate transaminase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, gamma-glutamyl transpeptidase (GGT), glucose, lactic acid dehydrogenase (LDH), magnesium, potassium, sodium, total bilirubin, total protein, uric acid, and phosphorus.

Coagulation laboratory evaluations include INR, PTT, PT.

PTH, TSAT, and Ferritin measures will also be assessed.

Hematology, serum chemistry, coagulation, PTH, TSAT, and Ferritin laboratory assessments and change from baseline to each of the post-baseline time points and week 52/ET will be summarized by analyte, visit, and treatment group using descriptive statistics (mean, median, SD, min, max, and number of subjects).

Shift tables for hematology, serum chemistry, and coagulation data to evaluate categorical changes from baseline will be presented. Shift from baseline laboratory measure will be presented as the number and percentage (n, %) of subjects who had shifted from baseline measure of Normal or Abnormal to a Normal or Abnormal post-baseline result at each post-baseline time point by analyte, cohort and overall.

Box and Whisker plots will be used to display changes in laboratory parameter values by treatment group over time.

Hematology, chemistry, coagulation, PTH, TSAT and Ferritin data will be windowed around the scheduled visits ± 4 weeks for the shift table analysis and change from baseline. Aside from week 1 which will be windowed as + 4 weeks only.

Phosphorus will be present at biomarker visits of Baseline, week 10, week 22 and week 52. All other data will be presented at scheduled visits.

Laboratory data will be provided in data listings.

10.7 Vital Signs and Weight

Vital sign measurements (heart rate, respiratory rate, SBP, DBP, temperature), weight, and change from baseline measurements will be summarized using descriptive statistics (mean, median, SD, min, max, and number of subjects) by visit, treatment group, and overall.

Vital signs measurements and weight will be defined as baseline if they are recorded prior to or up to 1 week after treatment start date (≤ study day 5).

Vital signs will be presented at scheduled visits.

10.8 12-Lead Electrocardiograms (ECG)

ECG data presentation will include QTc Interval Bazett and/or QTc Interval Fridericia, and overall interpretation of the ECG.

The following summaries will be generated for 12-Lead ECG:

1. Abnormal 12-Lead ECG results will be summarized as the number and percentage (n, %) of subjects who have an Abnormal Not Clinically Significant and who have an Abnormal Clinically Significant result by assessment, visit, and treatment group.
2. Shift table to evaluate categorical changes from baseline will be presented as the number and percentage (n, %) of subjects who have shifted from Normal, Abnormal Not Clinically Significant, or Abnormal Clinically Significant baseline measure to Normal, Abnormal Not Clinically Significant, or Abnormal Clinically Significant post-baseline result at each post-baseline time point by assessment, treatment group and overall.

QTcB and QTcF values will also be categorized for baseline and maximum post-baseline values and summarized by randomized treatment arm:

- <=450 msec
- >450 to 480 msec
- >480 to 500 msec
- >500 msec

Also, the maximum change in QTcB and QTcF from baseline will be categorized summarized by randomized treatment arm:

- <=30 msec

- >30 to 60 msec
- >60 msec

ECGs will be presented at scheduled visits. An ECG result recorded prior to or up to 1 week after treatment start date (≤ study day 5) can be considered as baseline.

10.9 Pregnancy Test

Pregnancy test data will be summarized by randomized treatment arm.

10.10 Physical Examination (PE) and Height

PE including height will be performed at screening and at Week 52/ET.

PE will be performed, and any findings will be assessed for clinical significance (CS). CS findings reported prior to study drug dosing will be recorded as Medical History; CS findings for all other PEs will be captured as AEs.

A summary of incidence of clinically significant findings (yes/no) at each scheduled visit will be provided as the number and percentage (n, %) of subjects within each category by treatment group and overall. Height will be summarized as a continuous variable using descriptive statistics (mean, median, SD, min, max, and number of subjects) by treatment group, and overall.

A data listing for physical examinations, whether or not clinically significant findings were determined, and height will be presented by subject.

10.11 Exposure and Compliance

The duration of exposure (weeks) to study drug, and actual volume infused (mL) of SNF472 will be summarized using descriptive statistics for the two treatment groups and overall. Duration of exposure will be calculated as [(date of last administration of study drug) – (date of first dose of study drug) + 1]/7.

Compliance (number of doses administered/number of doses scheduled based on the duration of the subject's participation) will be categorized as follows: 0-20%, >20-40%, >40-60%, >60-80%, >80-100%, >100-120%. Compliance categories will be summarized with descriptive statistics by treatment group and overall in the mITT population. The number of doses scheduled will assume a week consisting of 2 days expect 1 dose, a week consisting of 4 days expect 2 doses, and a week of 5 days expect 3 doses. 100% compliance over 52 weeks consists of 156 doses.

11 OTHER ANALYSES

11.1 Biomarker Analyses

Biomarker analyses will be performed at the time of or after the final analysis by a vendor selected by Sanifit and will be described in a separate SAP that will, when available, form a separate SAP or an addendum to the main SAP, i.e. this document.

11.2 Sub-Study Analyses

As described earlier in this document, the Sub-Study analysis will be described in a separate SAP that will, when available, form an addendum to the main SAP.

11.3 End-of-Study Analysis

A final analysis will be conducted after the last subject completes or discontinues the study and the resulting clinical database has been cleaned, quality checked, and locked.

12 CHANGES FROM THE PROTOCOL

The following changes have been made to the information provide in the protocol:

- The combined dose group vs placebo has been included as part of the primary objective in the sub-study.
- The combined dose group vs placebo has been chosen as the main study primary endpoint in place of the high dose vs placebo. Similarly, analysis of the primary efficacy endpoint has been focused on the combined dose group vs placebo contrast.
- For categorical analysis, specifically the analysis of the secondary exploratory endpoints b) and c), the protocol specified chi-square methodology. This has been replaced with exact logistic regression.
- Analysis of mortality has been extended from the Kaplan-Meier descriptive analyses described in the protocol to additionally include Cox regression analysis.
- Additional analyses have been added to investigate the number of patients with >15% progression in CAC volume score at Week 52.

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15 REFERENCES

Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med. 2011 Dec 10;30(28):3267-84

Appendix 1

The following definitions or descriptions apply to Sections 6.3 and 10.3.

Medical History

Category	Preferred Term
Diabetes Mellitus	Diabetes Mellitus
Diabetes Mellitus	Diabetes Mellitus Inadequate Control
Diabetes Mellitus	Type 1 Diabetes Mellitus
Diabetes Mellitus	Type 2 Diabetes Mellitus

Category	Preferred Term
Hypertension	Essential Hypertension
Hypertension	Hypertension
Hypertension	Malignant Hypertension
Hypertension	Secondary Hypertension

Category	Preferred Term
Peripheral Vascular Disease	Peripheral Vascular Disorder
Peripheral Vascular Disease	Peripheral Arterial Occlusive Disease
Peripheral Vascular Disease	Peripheral Artery Angioplasty
Peripheral Vascular Disease	Peripheral Artery Stenosis
Peripheral Vascular Disease	Peripheral Artery Thrombosis
Peripheral Vascular Disease	Peripheral Ischaemia
Peripheral Vascular Disease	Peripheral Revascularisation
Peripheral Vascular Disease	Peripheral Endarterectomy

Category	Preferred Term
Cerebrovascular Accident	Cerebrovascular Accident
Cerebrovascular Accident	Cerebrovascular Disorder
Cerebrovascular Accident	Ischaemic Stroke
Cerebrovascular Accident	Cerebral Infarction
Cerebrovascular Accident	Embolic Cerebral Infarction
Cerebrovascular Accident	Lacunar Infarction
Cerebrovascular Accident	Lacunar Stroke

Category	Preferred Term
Myocardial Infarction	Acute Myocardial Infarction
Myocardial Infarction	Myocardial Infarction

Category	Preferred Term
Coronary Artery Disease	Arteriosclerosis Coronary Artery

Coronary Artery Disease	Coronary Artery Disease
Coronary Artery Disease	Coronary Arterial Stent Insertion
Coronary Artery Disease	Coronary Artery Bypass

Category	**Preferred Term**
Heart Failure	Cardiac Failure Congestive
Heart Failure	Congestive Cardiomyopathy
Heart Failure	Cardiac Failure
Heart Failure	Cardiac Failure Acute
Heart Failure	Cardiac Failure Chronic
Heart Failure	Chronic Left Ventricular Failure
Heart Failure	Left Ventricular Dysfunction

Category	**Preferred Term**
Aortic Disease	Aortic Aneurysm
Aortic Disease	Aortic Aneurysm Repair
Aortic Disease	Aortic Arteriosclerosis
Aortic Disease	Aortic Calcification
Aortic Disease	Aortic Dilatation

Category	**Preferred Term**
Amputations	Leg amputation
Amputations	Arm amputation
Amputations	Foot amputation
Amputations	Toe amputation
Amputations	Finger amputation

Category	**Preferred Term**
Atherosclerotic Cardiovascular Disease (ASCVD)	Peripheral Vascular Disorder
Atherosclerotic Cardiovascular Disease (ASCVD)	Peripheral Arterial Occlusive Disease
Atherosclerotic Cardiovascular Disease (ASCVD)	Peripheral Artery Angioplasty
Atherosclerotic Cardiovascular Disease (ASCVD)	Peripheral Artery Stenosis
Atherosclerotic Cardiovascular Disease (ASCVD)	Peripheral Artery Thrombosis
Atherosclerotic Cardiovascular Disease (ASCVD)	Peripheral Ischaemia
Atherosclerotic Cardiovascular Disease (ASCVD)	Peripheral Revascularisation
Atherosclerotic Cardiovascular Disease (ASCVD)	Peripheral Endarterectomy
Atherosclerotic Cardiovascular Disease (ASCVD)	Cerebrovascular Disorder
Atherosclerotic Cardiovascular Disease (ASCVD)	Ischaemic Stroke
Atherosclerotic Cardiovascular Disease (ASCVD)	Cerebral Infarction
Atherosclerotic Cardiovascular Disease (ASCVD)	Embolic Cerebral Infarction
Atherosclerotic Cardiovascular Disease (ASCVD)	Lacunar Infarction

Atherosclerotic Cardiovascular Disease (ASCVD)	Lacunar Stroke
Atherosclerotic Cardiovascular Disease (ASCVD)	Acute Myocardial Infarction
Atherosclerotic Cardiovascular Disease (ASCVD)	Myocardial Infarction
Atherosclerotic Cardiovascular Disease (ASCVD)	Arteriosclerosis Coronary Artery
Atherosclerotic Cardiovascular Disease (ASCVD)	Coronary Artery Disease
Atherosclerotic Cardiovascular Disease (ASCVD)	Coronary Arterial Stent Insertion
Atherosclerotic Cardiovascular Disease (ASCVD)	Coronary Artery Bypass
Atherosclerotic Cardiovascular Disease (ASCVD)	Angioplasty

Medical History – Not included

Not Included Diabetes Mellitus

Diabetic Autonomic Neuropathy
Diabetic Foot
Diabetic Gastroparesis
Diabetic Nephropathy
Diabetic Retinopathy
Diabetic Vascular Disorder

Not Included in Hypertension

Procedural Hypertension

Not included in Peripheral Vascular Disease

Not Included in Cerebrovascular Accident

Transient Ischaemic Attack

Not Included in Myocardial Infarction

Acute Coronary Syndrome
Angina Pectoris
Myocardial Ischaemia

Not Included in Coronary Artery Disease

Arteriosclerosis

Not included in Heart Failure

Not included in Aortic Disease

Aortic Disorder

Aortic Stenosis
Aortic Stent Insertion

Not included in Amputations

Category	Medication Use at Baseline
Activated Vit D	Alfacalcidol
Activated Vit D	Calcitriol
Activated Vit D	Doxercalciferol
Activated Vit D	Hectoral
Activated Vit D	One alpha cacidol
Activated Vit D	Paricalcitol
Activated Vit D	Zemplar

Category	Medication Use at Baseline
Calcium-based phosphate binders	Calcium carbonate (many brands)
Calcium-based phosphate binders	Calcium acetate (many brands)

Category	Medication Use at Baseline
Sevelamer	Sevelamer hydrochloride
Sevelamer	Renagel
Sevelamer	Sevelamer carbonate
Sevelamer	Renvela
Sevelamer	Sevelamer

Category	Medication Use at Baseline
Lanthanum	Lanthanum carbonate
Lanthanum	Fosrenal
Lanthanum	Lanthanum

Category	Medication Use at Baseline
Sevelamer/Lanthanum	Sevelamer hydrochloride
Sevelamer/Lanthanum	Renagel
Sevelamer/Lanthanum	Sevelamer carbonate
Sevelamer/Lanthanum	Renvela
Sevelamer/Lanthanum	Sevelamer
Sevelamer/Lanthanum	Lanthanum carbonate
Sevelamer/Lanthanum	Fosrenal
Sevelamer/Lanthanum	Lanthanum

Category	Medication Use at Baseline
Iron-based phosphate binders	Sucroferric oxyhydroxide

Iron-based phosphate binders	Velphoro
Iron-based phosphate binders	Ferric citrate
Iron-based phosphate binders	Auryxia

Category	**Medication Use at Baseline**
Non-calcium-based phosphate binders	Sevelamer hydrochloride
Non-calcium-based phosphate binders	Renagel
Non-calcium-based phosphate binders	Sevelamer carbonate
Non-calcium-based phosphate binders	Renvela
Non-calcium-based phosphate binders	Sevelamer
Non-calcium-based phosphate binders	Lanthanum carbonate
Non-calcium-based phosphate binders	Fosrenal
Non-calcium-based phosphate binders	Lanthanum
Non-calcium-based phosphate binders	Sucroferric oxyhydroxide
Non-calcium-based phosphate binders	Velphoro
Non-calcium-based phosphate binders	Ferric citrate
Non-calcium-based phosphate binders	Auryxia

Category	**Medication Use at Baseline**
Statins	Atorvastatin
Statins	Lipitor
Statins	Atorvastatin Calcium
Statins	Fluvastatin
Statins	Lescol
Statins	Lescol XL
Statins	Lovastatin
Statins	Mevacor
Statins	Altoprev
Statins	Pravastatin
Statins	Pravachol
Statins	Pravastatin Sodium
Statins	Rosuvastatin
Statins	Crestor
Statins	Rosuvastatin Calcium
Statins	Simvastatin
Statins	Zocor
Statins	Pitavastatin
Statins	Livalo

Category	**Medication Use at Baseline**
Warfarin	Warfarin
Warfarin	Coumadin
Warfarin	Warfarin sodium

Category	**Medication Use at Baseline**
Calcimimetics	Cinacalcet
Calcimimetics	Sensipar
Calcimimetics	Mimpara
Calcimimetics	Cinacalcet hydrochloride
Calcimimetics	Etelcalcetide
Calcimimetics	Parsabiv
Calcimimetics	Etelcacetide hydrochloride

Category	**Preferred Term**
Safety Composite Endpoints (first of CV death, non-fatal MI, non-fatal stroke, or heart failure)	Cerebrovascular Accident
	Cerebrovascular Disorder
	Ischaemic Stroke
	Cerebral Infarction
	Embolic Cerebral Infarction
	Lacunar Infarction
	Lacunar Stroke
	Acute Myocardial Infarction
	Myocardial Infarction
	Cardiac Failure Congestive
	Congestive Cardiomyopathy
	Cardiac Failure
	Cardiac Failure Acute
	Cardiac Failure Chronic
	Chronic Left Ventricular Failure
	Left Ventricular Systolic Dysfunction
	Cardiac Arrest

Appendix 2

INTERIM ANALYSIS

A single, non-binding, interim analysis is planned for this study. It will include a futility analysis performed by [redacted]. The objective of the interim analysis is to determine whether there is a low probability of success of the trial. Further efficacy-related analyses are outlined in the Addendum. These analyses may be conducted at the option of Sanifit prior to the final analyses.

Futility Analysis

Approximately 270 subjects were planned to be randomized with N=190 expected to provide Week 52 data on the primary endpoint in the final analysis. A non-binding interim futility analysis will be conducted when approximately N=120 subjects (63% of N=190) have provided Week 52 data. The purpose of this interim analysis is to ascertain if the conditional power for achieving a statistically significant result in the final analysis of the two SNF472 doses combined would be low, ≤ 5%; if so the study may be declared futile and subject follow-up may consequently cease. There is no plan or intent to curtail follow-up at this interim for a positive efficacy finding. Conditional power is to be computed under the result observed at the interim as per Mehta and Pocock (2011).

The futility analysis will involve first performing the primary efficacy analysis on the mITT population. The primary efficacy endpoint is the change in log CAC volume scores between baseline (Week1, Day 1) and Week 52 as measured by CT scan. For this analysis, missing Week 52 CAC volume scores will be imputed using LOCF as described in section 7.1.2 of the SAP.

CAC volume score values will be log-transformed prior to analysis. The primary analysis will use an ANCOVA model with the change in log score (log 52-week score – log baseline score) as the dependent variable and with a fixed effect term for randomized treatment group and log CAC volume score at baseline as a covariate; the model will also be stratified by the randomization stratification factor, i.e.baseline CAC/Agatston score.

Least square (LS) means for each of the 3 treatment groups will be estimated and back transformed prior to presentation. The main contrasts of interest to assess treatment effect will be the difference in LS means between 1) high dose and placebo and 2) between the average of the high and low dose vs placebo. These contrasts will be on the log scale and will equal the treatment effect and standard error, and treatment effect will be back transformed prior to presentation. No p-values or 95% confidence intervals will be presented for the futility analysis.

The futility analysis will also involve a supportive multiple imputation analysis (Multiple Imputation I) to account for missing data. This analysis will be performed on the mITT population.

For this analysis, missing Week 52 CAC volume score will be imputed using SAS procedure MI within each treatment group (high dose, low dose and placebo) using distribution implied by the non-missing subject data for that treatment group. This will be done for all missing week 52 CAC volume scores including for subjects who discontinued early SAS code similar to the following will be used to impute missing values under the missing at random (MAR) assumption:

```
PROC MI data = <dataset _name>  SEED = <seed> NIMPUTE = 20 out = MI_Out;
```

```
        By TreatmentArm;
        CLASS  Strata;
        MONOTONE REG ( logWeek52 = TreatmentArm Strata logBaseline );
        VAR  Strata logBaseline logWeek52;
RUN;
```

Post imputation, each imputed datasets will be analyzed separately using ANCOVA method similar to the primary efficacy analysis (see Section 9.1.1). SAS code similar to the following will be used:

```
DATA CFB_Out;    SET MI_Out;   logCFB = logWeek52 - logBaseline;    RUN;

PROC GLM DATA = CFB_Out;
        CLASS TreatmentArm Strata;
        MODEL logCFB =  TreatmentArm Strata logBaseline/ SOLUTION;
        ESTIMATE 'TreatmentArm 1 vs 3' TreatmentArm 1 -0 -1;
        ESTIMATE 'TreatmentArm 2 vs 3' TreatmentArm 0 1 -1;
        ESTIMATE 'TreatmentArm 1 and 2 vs 3' TreatmentArm 0.5 0.5 -1;
        BY  _Imputation_;
        ODS OUTPUT ESTIMATES = glm_est;
RUN;
```

The SAS procedure MIANALYZE will be used to combine the 20 sets of estimates by Rubin's rules . SAS code similar to the following will be used:

```
DATA glm_est (DROP=parameter1);
        SET glm_est(RENAME = (parameter= parameter1));
        parameter = COMPRESS(parameter1);
RUN;

PROC MIANALYZE PARMS = glm_est;
        MODELEFFECTS TreatmentArm1vs3 TreatmentArm2vs3 TreatmentArm1and2vs3  ;
RUN;
```

LS means for each of the 3 treatment groups will be estimated and back transformed prior to presentation. The main contrasts of interest to assess treatment effect will be the difference in LS means between high dose and placebo and between the average of the two doses vs placebo. These contrasts will be presented on the log scale and will equal the treatment effect and standard error, and treatment effect will be back transformed prior to presentation. No p-values or 95% confidence intervals will be presented for the futility analysis.

The futility analysis will also involve a second supportive multiple imputation analysis (Multiple Imputation II) to account for missing data. This analysis will be performed on the mITT population.

For this analysis, missing Week 52 CAC volume score will be imputed using SAS procedure MI for all treatment groups using the distribution implied by the non-missing subject data within the placebo group. This will be done for all missing week 52 CAC volume scores including for subjects who discontinued early SAS code similar to the following will be used to impute missing values under the missing not at random (MNAR) assumption:

```
PROC MI data = <dataset _name>  SEED = <seed> NIMPUTE = 20 out = MI_Out;
        CLASS TreatmentArm Strata;
```

```
        MONOTONE REG ( / details);
        MNAR MODEL ( logWeek52 / MODELOBS = (TreatmentArm='3' ) );
        VAR Strata logBaseline logWeek52;
RUN;
```

Post imputation, each imputed datasets will be analyzed separately using ANCOVA method similar to the primary efficacy analysis (see Section 9.1.1). The 20 sets of estimates will then be combined by Rubin's rules using SAS procedure MIANALYZE. SAS code similar to the codes presented in Section 9.1.4.2 will be used.
LS means for each of the 3 treatment groups will be estimated and back transformed prior to presentation. The main contrasts of interest to assess treatment effect will be the difference in LS means between high dose and placebo and between the average of the two doses vs placebo. These contrasts will be on the log scale and will equal the treatment effect and standard error, and treatment effect will be back transformed prior to presentation. No p-values or 95% confidence intervals will be presented for the futility analysis.

These results from the primary efficacy analysis along with the results from the supportive multiple imputation analyses will be provided to an independent statistician selected by the Sponsor who will compute the conditional power (CP) using Mehta and Pocock methods.

In addition, the [redacted] unblinded statistician will conduct these same conditional power analyses using the following SAS code:

```
cp = 1- probnorm( ( probit(1-&a)*sqrt(n2) - tvalue*sqrt(n1) ) / sqrt(n2-n1) -
tvalue*sqrt((n2-n1)/n1) );

For this syntax, a=0.025, n1=number of subjects observed at interim,  n2=190
and tvalue=observed treatment effect on the log scale.
```

The independent statistician will provide the IDMC with the following information:

- For the mITT analysis
    1. CP for of (high dose+low dose)/2 vs placebo is (a) ≤5% or (b) >5%
    2. CP for of high dose+ vs placebo is (a) ≤5% or (b) >5%
- For the supportive MI analysis (MI I)
    1. CP for of (high dose+low dose)/2 vs placebo is (a) ≤5% or (b) >5%
    2. CP for of high dose+ vs placebo is (a) ≤5% or (b) >5%
- For the supportive MI analysis (MI II)
    1. CP for of (high dose+low dose)/2 vs placebo is (a) ≤5% or (b) >5%
    2. CP for of high dose+ vs placebo is (a) ≤5% or (b) >5%

Focus is to be placed upon 1. the mITT CP for of (high dose+low dose)/2 vs placebo followed by 2. CP for items 3-6 above are provided as supportive information.

Pharmacokinetic and Pharmacodynamic Analyses

PK and PD analyses will be performed at the time of the interim analysis and final analysis by a vendor selected by the Sponsor and will be described in a separate SAP that will be described in a separate SAP that will, when available, form a separate SAP or an addendum to the main SAP.