NOVARTIS

Clinical Development

ACZ885M/Canakinumab

Clinical Trial Protocol CACZ885M2301

A randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP

Authors:	Thuren,Tom, MacKenzie,Michele, Holzhauer,Björn, Ridker, Paul, Glynn, Robert, Frusciante, Karen

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List of abbreviations

ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CAPS	Cryopyrin-Associated Periodic Syndromes
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CRF	Case Report/Record Form
CPO	Country Pharma Organization
CRO	Contract Research Organization
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
GFR	Estimated Glomerular Filtration Rate
EOS	End of Study
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
GWA	Genome-wide association
HbA1c	Glycosylated hemoglobin
HIV	Human Immunodeficiency Virus
hsCRP	High Sensitivity C-Reactive Protein
IA	Interim Analysis
IB	Investigators Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunogenicity

IL-1β	Interleukin 1 Beta
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IVRS/IWRS	Interactive Voice Response System/ Interactive Web Response System
LDL	Low density lipoprotein
LFT	Liver Function Test
MACE	Major CV Disease Events
MFSI-SF	Multi Dimensional Fatigue Symptom Inventory-Short Form
MI	Myocardial Infarction
MRS	Modified Rankin Scale
NOD	New Onset Diabetes
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol Set
PPD	Purified protein derivative
PRO	Patient Reported Outcomes
PTCA	Percutaneous transluminal coronary angioplasty
PVD	Peripheral Vascular Disease
QFT-g	QuantiFERON-TB Gold
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SBP	Systolic Blood Pressure
s.c.	Subcutaneous
SOC	System Organ Class
SIS-16	Stroke Impact Scale
SMQ	Standardized MedDRA Queries
T2DM	Type 2 Diabetes Mellitus
TB	Tuberculosis
TIA	Transient Ischemia Attack

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug or placebo used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Amendment 3

Amendment rationale

The rationale for this amendment is, in agreement with health authorities, to adjust a treatment arm and to ensure the integrity of the study. Enrollment for this trial has not yet started.

Changes to the protocol

- In amendment 1 an early high dose regimen was selected for both the 150 mg and 300 mg arms whereby each of these doses would be administered twice, over two week period, at randomization (month 0) and at week 2 (month 0.5). To provide a greater separation between the active-dose arms, the early high dose regimen in the 150 mg arm has been removed. This is in agreement with health authority feedback.
- An exploratory objective has been added to examine the impact of the early high dose regimen between 300 mg arm (with the early high dose administered) and the 150 mg arm (with no early high dose administered) on clinical cardiovascular events.
- To maintain the integrity of the study the data from the interim analyses of T2DM related glycemic control parameters will not be shared with Novartis management as noted in Section 3.5. This is compliant with health authority feedback.

The changes will be implemented throughout the protocol. Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions. A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Summary of previous amendments

Amendment 2

Short summary of the amendment rationale and major changes

In the original protocol all deaths, cardiovascular and non-cardiovascular, were reported as potential endpoints and were adjudicated by cardiovascular clinical adjudication committee. Only those deaths, which the adjudication committee determined to be non-cardiovascular deaths, were reported as SAEs after adjudication was completed.

In order to comply with the recent 21 CFR Parts 312 and 320 regulation and draft FDA guidance on Safety Reporting Requirements for INDs and BE/BA Studies, section on reporting clinical endpoints (21 CFR 312.32 (c)(5)), protocol section 7.2 has been revised to assure that certain selective study drug related non-cardiovascular deaths will be reported both as study endpoints and SAEs as soon as study site has been notified of such events without waiting for adjudication committee to complete the adjudication process. This revised SAE

reporting procedure fulfills requirements in the above mentioned regulation and draft FDA guidance.

In addition, the definition of pre-diabetes was revised to include impaired fasting glucose, FPG 100-125 mg/dL, as a criterion together with the original criterion of HbA1c 5.7-6.4% based on FDA feedback on IND filing of this protocol.

Amendment 1

Short summary of the amendment rationale and major changes

In the original protocol, the dose of canakinumab that provided near maximal biomarker suppression was selected as 150 mg quarterly, and an additional lower dose was selected below this level at 50 mg quarterly. However, as more efficacy data has been analyzed and safety data has accumulated for canakinumab in rheumatoid arthritis and gout patients, safety across a wide range of doses has continued to show a well tolerated and safe profile following higher dose administration. Thus the opportunity has arisen for the CACZ885M2301 protocol to evaluate a higher canakinumab dose since the dose needed for adequate IL-1β neutralization within the plaque or systemically in inflammation-based atherosclerosis is not established. Therefore, a higher dose might deliver greater efficacy than originally selected doses. Thus, as indicated here prior to randomization of any trial participants, the doses to be evaluated in CACZ885M2301 will be placebo s.c. quarterly, 150 mg canakinumab s.c. quarterly and 300 mg canakinumab s.c. quarterly. In addition, currently available safety data provides the opportunity to introduce an early higher dose administration in order to achieve early anti-inflammatory benefit in this high risk cardiovascular population. This induction period provides drug administration twice over a 2 week period and seeks to achieve optimal IL-1β suppression early to provide optimal clinical benefit. Thus, the CACZ885M2301 trial regimens will consist of:
(a) placebo s.c. at randomization (month 0), placebo s.c. at week 2 (month 0.5), placebo s.c. at week 12 (month 3), and then placebo s.c. quarterly;
(b) canakinumab 150 mg s.c. at randomization (month 0), canakinumab 150 mg s.c. at week 2 (month 0.5), canakinumab 150 mg s.c. at week 12 (month 3), and then canakinumab 150 mg s.c. quarterly; and
(c) canakinumab 300 mg s.c. at randomization (month 0), canakinumab 300 mg s.c. at week 2 (month 0.5), canakinumab 300 mg s.c. at week 12 (month 3), and then canakinumab 300 mg s.c. quarterly.

Advantages of a 300 mg quarterly dose rather than the 50 mg quarterly dose and an additional early dose of canakinumab (either 150 mg or 300 mg) are supported by data that de-couples the biomarker dose effect from gene expression dose effect. The proposed dose regimens are aimed to provide optimal suppression of potential auto-induction of IL-1β and greater early suppression of IL-1β related gene expression. IL-1β auto-induction has been shown in human mononuclear blood, vascular endothelial and vascular smooth muscle cells in vitro and in rabbits in vivo where IL-1 has been shown to induce its own gene expression and circulating IL-1β level (Dinarello et al. 1987, Warner et al. 1987a, and Warner et al. 1987b). These studies suggested that IL-1 induced IL-1 gene expression may provide a positive feedback mechanism in the pathogenesis of atherosclerosis and promote atherosclerosis. This

consequently suggests that suppression this feedback mechanism may provide benefits in the atherosclerotic lesion. To accommodate this change in administration of canakinumab, a week 2 visit for drug administration and safety assessments was added to the study visit schedule. The change in dosing regimen necessitated an update to the definition of the safety set. The safety set definition was based on the new Novartis Cardiovascular Clinical Science Unit standards. Similarly, the definition of the censoring date was aligned with these standards. This definition reflects that if there was contact with a patient without the patient attending a visit, then the visit date – in the absence of other information – should be the date of the last contact with the patient.

In addition, the following errors and omissions in the original protocol were corrected:

- Pharmacogenomics information was added to the protocol and study visit schedule
- Troponin I and creatine kinase MB fraction were added for patients with elevated total creatine kinase
- Genetics sample storage will be at the Central Laboratory
- SAE reporting instructions were corrected to direct investigators to follow instructions provided in the investigator folder
- Supraventricular tachycardia and atrial fibrillation definitions were added to the protocol
- CABG-MI definition was updated to follow universal MI definition (Thygesen et al 2007)
- Diabetes related definitions used in stratification section were updated
- PK/PD/IG sampling time-points were updated
- HOMA calculation was removed
- A confirmation of elevated ALT/AST and total bilirubin is no longer required at screening

Protocol synopsis

Title of study: A randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP

Purpose and rationale: The purpose of this trial is to test the hypothesis that canakinumab treatment of patients with MI at least one month prior to study entry and elevated hsCRP will prevent recurrent cardiovascular events. A secondary hypothesis, that canakinumab treatment in patients with MI and pre-diabetes, will prevent new onset diabetes (NOD) will also be tested. The trial is pivotal for registration for canakinumab for cardiovascular risk reduction.

Objectives:

Primary Objective

The primary objective of this clinical trial is to demonstrate the superiority of at least one dose of canakinumab compared to placebo in reducing the risk of recurrent major cardiovascular disease events (cardiovascular death, non-fatal MI and stroke) in a population of clinically stable post-MI patients with elevated hsCRP receiving standard of care.

Key and other secondary objectives

- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of CV death, non-fatal MI, stroke, and hospitalization for unstable angina requiring unplanned revascularizations.
- To demonstrate superiority of canakinumab compared to placebo on the endpoint of new onset type 2 diabetes among those with pre-diabetes at randomization
- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of all-cause mortality, non-fatal MI and stroke.
- To demonstrate superiority of canakinumab as compared to placebo on the endpoint of all-cause mortality
- To evaluate the long-term safety of canakinumab therapy in a placebo-controlled setting

Exploratory Objectives

- To explore whether canakinumab compared to placebo reduces the risk of other cardiovascular disorders with a known inflammatory component:
  - Composite of deep vein thrombosis/pulmonary embolism
  - Supraventricular tachycardia/atrial fibrillation
  - Stent thrombosis (probable or definite)
  - Hospitalization or prolongation of hospitalization due to heart failure
  - Major coronary events composite (CHD death, non-fatal MI)
  - Total vascular events composite

  - Coronary revascularization procedures (PCI or CABG)
  - Stroke by etiology
- To explore the dose response relationship and the effects of induction dosing in terms of cardiovascular endpoints.
- To explore whether canakinumab compared to placebo reduces nephropathy as assessed by urinary albumin/creatinine ratio in patients with T2DM or pre-diabetes at baseline
- To explore whether canakinumab compared to placebo improves glycemic control among those with type 2 diabetes
- To explore whether canakinumab compared to placebo standard of care affects biomarkers of cardiovascular and diabetes risk, including inflammatory biomarkers, glycemic control markers, β-cell function markers
- To explore whether canakinumab as compared to placebo affects patient reported outcomes of tiredness, physical function and performance function and improves health status as assessed by the EQ-5D Quality of Life (QOL) assessment.
- To perform exploratory pharmacogenetic and pharmacogenomic assessments to examine whether individual genetic variation in genes relating to drug metabolism, major cardiovascular events, type 2 diabetes, and the drug target pathway confer differential response to canakinumab.

Population: Participants eligible for this trial will include male and non-child-bearing potential female patients age 18 years and older who (a) have suffered a documented acute myocardial infarction at least 30 days before randomization and (b) have evidence of systemic inflammation on the basis of a hsCRP $\geq$ 2 mg/L despite the use of standard of care post-MI medical therapies. Standard of care post-MI background therapy includes, but is not limited to, lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as appropriate.

The trial will be an event-driven global trial conducted in the outpatient setting. It is anticipated that approximately 694 cardiovascular endpoints will accrue during the course of the trial (see Section 9.7 for Power Calculations). To accomplish this goal, it is expected that around 14,600 patients will need to be screened in order to randomize approximately 7,302 patients.

Key Inclusion/Exclusion criteria:

Inclusion

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male, or Female of non-child-bearing potential
3. Age $\geq$ 18 years at Visit 1.
4. Documented spontaneous MI (diagnosed according to the universal MI criteria with or without evidence of ST segment elevation) at least 30 days before randomization. (Thygesen et al 2007)

- Diagnosis of prior MI should be based on medical history of clinical symptoms consistent with myocardial ischemia associated with elevation of cardiac biomarkers above the 99th percentile of the upper reference limit (preferably troponin) OR development of new pathological Q waves regardless of symptoms (See Appendix 15) or ECG changes associated with prior myocardial infarction (Thygesen et al 2007). For details, refer to the Universal Definition of MI (Thygesen et al 2007). Patients with MI resulting from PCI or CABG will not be eligible

5. Have an hsCRP ≥ 2 mg/L at screening (Visit 1) (which is at minimum of 28 days after qualifying MI or after any PCI performed separately from qualifying MI) on stable (at least 4 weeks) long-term medications.

Exclusion

Patients fulfilling any of the following criteria are not eligible for inclusion in this trial:

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/ml)
2. Women of child-bearing potential defined as all women physiologically capable of becoming pregnant, UNLESS they are
   - Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml (for US only: and estradiol < 20 pg/mL) or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormonal level assessment is she considered not of child bearing potential.
3. Any of the following concomitant diseases
   - Planned coronary revascularization (PCI or CABG) or any other major surgical procedure.
   - Major non-cardiac surgical or endoscopic procedure within past 6 months to Visit 1
   - Multi-vessel CABG surgery within the past 3 years
   - Symptomatic patients with Class IV heart failure (HF) (New York Heart Association [NYHA].
   - Uncontrolled hypertension (defined as an average SBP >160 mmHg or an average diastolic blood pressure (DBP) >100 mmHg at Visit 1. Patients are allowed to be re-evaluated, at the discretion of investigator for this criterion if anti-hypertensive therapy has been started or increased as a result of initial screening blood pressure above these limits. (Mancia et al 2009).
   - Uncontrolled diabetes as defined by the investigator

- Nephrotic syndrome or eGFR < 30 mL/min/1.73 m^2 per MDRD formula or kidney transplant (regardless of renal function), Visit 1
- Known active or recurrent hepatic disorder (including cirrhosis, hepatitis B and hepatitis C, or ALT/AST levels > 3 times ULN or total bilirubin > 2 times ULN) ,Visit 1
- Prior malignancy other than basal cell skin carcinoma

4. A history of alcohol and/or substance abuse that could interfere with the conduct of the trial
5. History or evidence of active tuberculosis (TB) infection at Visit 1 or one of the risk factors for tuberculosis such as but not limited or exclusive to:
   - History of any of the following: residence in a congregate setting (e.g. jail or prison, homeless shelter, or chronic care facility), substance abuse (e.g. injection or non-injection) health-care workers with unprotected exposure to patients who are at high risk of TB or patients with TB disease before the identification and correct airborne precautions of the patient

   or

   - Close contact (i.e. share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours)) with a person with active pulmonary TB disease within the last 12 months.
6. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection, at Visit 1, determined as defined by local guidelines/ local medical practice (see also below for determination of tuberculosis status). If presence of tuberculosis is established then treatment (according to local guidelines) must have been completed prior to randomization.
7. Patients with suspected or proven immunocompromised state, including (a) those with evidence of Human Immunodeficiency Virus (HIV) infection; Patients on anti-retroviral therapy are excluded (b) those with any other medical condition which in the opinion of the investigator places the patient at unacceptable risk for participation in immunomodulatory therapy; or (c) those requiring systemic or local treatment with any immune modulating agent in doses with systemic effects e.g. high dose oral steroids. Topical, inhaled, local steroid use in doses that are not considered to cause systemic effects are permitted.
8. Live vaccinations within 3 months prior to the randomization visit or live vaccinations planned during the trial.
9. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
10. Patients who have received an investigational drug or device within 30 days (inclusive) of Visit 1, or who are expected to participate in any other investigational drug or device study during the conduct of this trial, except for patients who have an investigational treatment eluting stent (DES), provided that they have completed the DES trial. FDA/country-specific drug regulatory authority approved DES devices are permitted.

11. Any biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, tocilizumab)
12. Any life threatening condition with life expectancy < 5 years, other then vascular disease that might prevent the patient from completing the study

Investigational and reference therapy:
Patients will be assigned to one of the following 3 treatment arms in a ratio of 1:1:1

- Canakinumab 150 mg s.c. at randomization, placebo s.c. at week 2, 150 mg s.c. at week 12, and thereafter 150 mg s.c. quarterly
- Canakinumab 300 mg s.c. at randomization, 300 mg s.c. at week 2, 300 mg s.c. at week 12, and thereafter 300 mg s.c. quarterly
- Placebo s.c. at randomization, at week 2, at week 12, and thereafter quarterly

For patients who are unable to tolerate the protocol-specified dosing intervals, dose interruptions are permitted in order to keep the patient on study drug. Patients are encouraged to continue study medication; however; they are allowed to interrupt and re-start medication at any time during the study at the discretion of the investigator.
Study design: The study is a Phase 3 multi-center, randomized, parallel group, placebo-controlled, double-blind event-driven global clinical trial to evaluate the benefit of quarterly subcutaneous canakinumab doses compared to placebo among stable post-MI patients receiving standard of care therapy who have been selected for an elevated inflammatory burden as determined by hsCRP $\geq$ 2 mg/L. The index qualifying MI must have occurred at least 30 days prior to randomization. Standard of care post-MI background therapy includes but is not limited to appropriate lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as defined by local guidelines.

Screening will take place no earlier than 28 days after the index MI and on stable (at least 4 weeks) long term medication. Evaluations will include hsCRP and determination of tuberculosis status among other measurements and procedures. After screening visit, patients may be randomized, as soon as, results from screening laboratory and other studies are available. However, this can be no earlier than 30 days after the index MI. For patients who underwent PCI at different hospital admission than the qualifying MI; screening can be initiated no earlier than 28 days following this procedure. For patients who have history of CABG; screening can be initiated no earlier than 3 years after the procedure regardless of timing of the qualifying MI.

Randomization will be stratified by time since most recent index myocardial infarction with 50% of the population in each strata (30 days to <6 months and ≥6 months). The Steering Committee and Sponsor will monitor the patient profiles during recruitment phase and may increase or restrict enrollment of certain sub-groups of patients to avoid imbalances. There will be no upper limit for post MI for inclusion into the trial. The trial is event driven and designed to complete when a total of 694 patients have experienced a primary cardiovascular endpoint. Double blind treatment will be continued until the target number of primary cardiovascular endpoints has been reached. Sites will then be notified to have all patients return to complete an EOS visit. The elapsed calendar time to reach conclusion of the study is estimated to be a total of 4.5 years of treatment and follow-up from the start of enrollment in

the trial to the occurrence of 694 confirmed cardiovascular events. These estimates are based on the assumption that the time necessary to complete enrollment in the study will be approximately 18 months.

Interim analyses (IA) of efficacy, futility and safety will be carried out during the study in order to avoid exposing study patients to ineffective treatment or undue risks or to allow study discontinuation in case of overwhelming efficacy. Two interim analyses of efficacy will be performed when approximately 50% of the target number of patients with primary endpoints have been accumulated and the second one when approximately 75% of the planned number of patients with primary endpoints are available.

Following a successful completion of this trial all patients who are either normoglycemic or have T2DM will be enrolled in an open label follow-up study where participants will be treated with canakinumab in order to determine long term safety and efficacy of canakinumab treatment. Patients with pre-diabetes at the end of this trial (last in trial HbA1c 5.7-6.4% or FPG 100-125 mg/dL) will first enter into the 6 month washout phase followed by the open label follow-up study including re-starting canakinumab treatment. This safety follow-up study will collect safety events to be determined based on canakinumab profile in the main trial and major cardiovascular adverse events as defined in the primary endpoint of the main trial at bi-annual visits. An extension protocol with detailed study information including length of the follow-up will be developed for the open label follow-up study.

Efficacy assessments:

Primary efficacy assessment:
The primary endpoint is defined as the time to the first event of a major cardiovascular event (MACE) occurring during the double-blind treatment period, which is a composite of CV death, non-fatal MI, and stroke. An independent adjudication committee that is blinded to treatment assignments will review and adjudicate all clinical events that constitute the composite endpoint.

Key secondary efficacy assessments:
Key secondary efficacy assessments will comprise:

- Time to first event of a composite cardiovascular endpoint consisting of the primary endpoint, and hospitalization for unstable angina requiring unplanned revascularization
- Time to new onset type 2 diabetes among those with pre-diabetes at randomization (time to NOD)

Other secondary efficacy assessments:
Other secondary efficacy assessments will comprise

- Time to first event of, non-fatal MI, stroke and all-cause mortality composite
- Time to all-cause mortality

Exploratory efficacy assessments
Exploratory efficacy assessments are described in (Section 6.4.2) of the clinical study protocol.

Safety Assessments*:*

- Laboratory evaluations
- Height and Weight
- Adverse events and serious adverse events, including cardiovascular events, malignancies, and infections
- Discontinuation due to AEs
- Hypoglycemia events
- Injection site reactions
- Physical Examination
- Biomarkers
- Vital Signs
- ECG

Serious allergies/immunological events, serious infections, and malignancies adverse events will be monitored carefully during this trial because these adverse events represent hypothetical mechanism of action related risks of canakinumab therapy.

Other Assessments:

- Assessment of Glycemic Control for T2DM
- Stroke Functional Assessment Sub-Study
- The Modified Rankin Scale, MFSI-SF, SIS-16, EQ-5D,SF-36 Health State Classification, Visual Analogue Scale 'Thermometer'
- Pharmacokinetics, pharmacogenetics, pharmacogenomics, and other biomarkers

Data analysis:
The primary statistical hypotheses are:

- H_{11}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 150 mg dose group is greater than or equal to that in the placebo group
- H_{21}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 300 mg dose group is greater than or equal to that in the placebo group

Each tested versus the one-sided alternative that the hazard rate is smaller for the respective active dose group than in the placebo group.

These hypotheses will be tested by comparing each dose to placebo with a log-rank test stratified by time since index MI using Peto's exact method (Peto 1972) for handling ties on the FAS according to the intent-to-treat principle. The family-wise error rate will be controlled at the two interim analyses and the final analysis using a closed testing procedure that initially assigns all the available significance level equally to the two primary null hypotheses relating to the two doses. Key secondary endpoints for a dose are only tested after the rejection of the primary null hypothesis for that dose.

A fixed Bonferroni split of the one sided alpha will be used to account for the two efficacy interim analyses and the final analysis, with a significance level of 0.01% for the first efficacy interim analysis, 0.04% for the second efficacy interim analysis and 2.45% for the final

analysis. In this fashion the family-wise type I error rate will be controlled at the one-sided 2.5% level.

The hazard ratios and their associated confidence intervals will be estimated by means of a Cox proportional-hazards model stratified by time since index MI (< 6 months, ≥ 6 months) using treatment (canakinumab doses and placebo) as a factor in the model using Peto's exact method (Peto 1972) for handling ties. Kaplan-Meier plots will be presented to summarize the time to first event in the composite endpoint, by presenting the time-dependent cumulative frequency and percentage of patients who reach the primary composite endpoint by treatment group.

The components of the composite primary efficacy endpoint (CV death, fatal or non-fatal MI, fatal or stroke) will also be analyzed individually in order to evaluate their contributions to the overall treatment effect.

Based on the FAS, all key secondary efficacy variables will be analyzed with a log-rank test stratified by time since index MI and displayed by means of Kaplan-Meier plots according to treatment.

The secondary efficacy variable corresponding to new onset type 2 diabetes in patients with pre-diabetes at randomization will be the time from randomization to the first occurrence of repeated FPG ≥ 126 mg/dL or of a repeated HbA1c ≥ 6.5% or of the start of new anti-diabetic medication. Due to the discrete nature of the time points when new onset of type 2 diabetes can be determined, events identified at the same visit time point for different patients will be considered as tied events and Peto's (Peto 1972) exact method for handling ties will be used.

Exploratory time-to-event outcomes will be analyzed using Cox regression models including treatment with time since index MI as a stratification variable, along with Kaplan-Meier analyses. Exploratory continuous outcome variables (i.e. change from baseline of HbA1c, biomarkers, and patient reported outcomes, etc.) will be analyzed using both a repeated measures analysis of covariance adjusted for baseline value, as well as descriptively.

Safety

The incidence of adverse events (new or worsened) will be summarized by primary system organ class (SOC), preferred term, severity and relationship to study drug. The incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term. Selected SAEs will be narrated.

The incidence of adverse events related to cardiovascular events in constellations relevant for a description of safety and death, as well as serious infections and malignancy will be specifically investigated. Appropriate time to event assessments will be used if warranted.

Laboratory data will be summarized by shift tables and categorical analyses using extended normal ranges if thresholds of interest are identified based on baseline to most extreme post-baseline value, with summary statistics of raw and change from baseline by visits. Furthermore, notable values will be flagged in data listings.

Sample Size Calculation

With a sample size of 7,302 randomized patients recruited within 1½ years of study initiation and assigned in a 1:1:1 allocation ratio to canakinumab 150 mg, canakinumab 300 mg, and placebo it is expected that 694 patients will experience a primary endpoint within 4½ years of study initiation. 694 endpoints are necessary to achieve a power of approximately 90% to demonstrate the superiority of at least one dose of canakinumab compared to placebo on the primary endpoint assuming a relative hazard reduction of 23.9% for both active doses.

1 Introduction

1.1 Background

Atherosclerosis is a disease characterized by chronically high inflammatory state. Arterial inflammation and endothelial dysfunction play key roles at all stages of the atherothrombotic process. Inflammatory mediators are intimately implicated with the cascade of events leading to atherosclerotic plaque initiation, progression and rupture. Vascular endothelial cells express a variety of adhesion molecules that recruit monocytes when chronically exposed to noxious stimuli or pathological conditions. Adverse conditions such as hyperlipidemia are associated with enrichment of a pro-inflammatory subset of monocytes. These monocytes apparently enter the intima under the influence of chemotactic stimuli and engulf modified low density lipoprotein (LDL) and cholesterol crystals (Duewell et al 2010). The material internalized by phagocytes induces phagolysosomal damage and subsequent leakage of contents into cytosol to activate inflammasomes and caspase 1, and consequently the generation of interleukin-1b (IL-1β) from pro-interleukin-1β.

Interleukins are key mediators in the chronic vascular inflammatory response in cardiovascular (CV) disease and have been demonstrated in animal models and in humans to be potent modulators of pro-inflammatory processes. The fact that these cytokines and their receptors are highly expressed and are functional in almost all cell types implicated in the pathogenesis of atherosclerosis including smooth muscle cells, certain subset of macrophages and T cells as well as endothelium support the role of interleukins in vascular disease. For example, IL-1β is a potent smooth muscle cell mitogen, an activator of endothelial cells and increases extra cellular matrix and collagen deposition, which plays a role in plaque burden and arterial thickening. Furthermore, lack of IL-1β or ablation of IL-1 receptor has been shown to decrease severity of atherosclerosis in apoE deficient mice. Thus, antagonism of the IL-1β mediated inflammation is a primary and attractive target for ameliorating the vessel wall inflammation associated with atherosclerosis.

Canakinumab (ACZ885) is a fully human monoclonal anti-human IL-1β antibody of the IgG1/k isotype, being developed for the treatment of IL-1β driven inflammatory diseases. It is designed to bind to human IL-1β and thus blocks the interaction of this cytokine with its receptors. The antagonism of the IL-1β mediated inflammation using canakinumab in lowering high sensitivity C-reactive protein (hs-CRP) and other inflammatory marker levels has shown an acute phase response in patients with Cryopyrin-Associated Periodic Syndrome (CAPS) and rheumatoid arthritis (data on file). This evidence has been replicated in patients with type 2 diabetes mellitus (T2DM) using canakinumab (data on file), and with other IL-1β antibody therapies in development.

Therefore, canakinumab is expected to reduce the risk of future occurrence of major cardiovascular events in patients with recent past myocardial infarction (MI) by preventing IL-1β mediated vascular wall inflammation and endothelial dysfunction.

Atherosclerotic vascular disease is the primary cause of morbidity and mortality in individuals with and without T2DM. The progression of atherosclerosis from endothelial dysfunction to vascular occlusion or to plaque rupture is the underlying mechanism responsible for many

debilitating and life-threatening diseases such as MI, stroke and peripheral vascular disease (PVD). These diseases occur at higher frequency in T2DM patients and continue to increase despite use of current optimal therapies. There is also higher mortality rate after first MI in patients with T2DM compared to those without T2DM. Mortality associated with impaired glucose tolerance is 1.96 times higher compared to normal glucose tolerance. Thus, novel therapies that may improve vascular function, decrease atherosclerotic burden, and translate to a decrease in cardiovascular events would fill a significant unmet medical need.

T2DM is also a disease that is characterized by a high inflammatory state. Pre-clinical data suggests IL-1β is of key importance in the progressive functional impairment and destruction of β-cells in type 2 diabetes. Pancreatic β cells secrete IL-1β in response to elevated glucose exposure promoting further impairment of cellular viability via an autocrine action. IL-1β antagonism inhibits β cell death, promotes β cell proliferation, potentiates β cell glucose-induced insulin secretion and improves insulin sensitivity. Blocking IL-1β activity with an IL-1 receptor antagonist as well as a neutralizing IL-1β antibody in clinical trials reduced HbA1c. Neutralization of IL-1β activity in the pancreatic islets is thus emerging as an attractive target for the treatment and prevention of type 2 diabetes. For T2DM prevention canakinumab's primary direct action is expected to prevent the IL-1β mediated destruction of pancreatic β-cells and thus prevent or delay progression of disease, which to date is a completely unmet need.

Therefore, canakinumab is expected to prevent new onset T2DM in patients with a recent past MI and that are pre-diabetic, and who are at risk of developing T2DM.

As demonstrated in a comprehensive 2010 meta-analysis of 54 prospective cohort studies, the inflammatory biomarker hsCRP is an independent risk factor for future cardiovascular events that (a) has a magnitude of effect similar to or larger than that of blood pressure or cholesterol and (b) has long-term stability and reproducibility at least as good as these widely-accepted risk factors (Kaptoge et al 2010). Abundant clinical trial data further demonstrate that persistent elevations of hsCRP are a major risk factor of recurrent vascular risk following myocardial infarction; for example, as demonstrated in the PROVE IT-TIMI 22 (Ridker et al 2005) and A-to-Z (Morrow et al 2006) trials. In both trials patients with known vascular disease and persistent elevation of hsCRP were at roughly double the risk for recurrent events compared to those with normal hsCRP levels. Further, stratification by hsCRP has proven highly effective in determining populations in who added cardiovascular benefits are observed with the use of efficacious lipid lowering agents, which also possess, anti-inflammatory properties. This has been proven in primary prevention studies as including the AFCAPS/TexCAPS (Ridker et al 2001) and JUPITER trials (Ridker et al 2008, Ridker et al 2009) as well as in the setting of congestive heart failure (CHF) in the CORONA trial where efficacy of intervention was seen only among those with hsCRP $\geq$2 mg/L. Indeed, in this latter example, had stratification been done by hsCRP on an a priori basis, the trial would have been reported out as an overwhelming positive rather than as a null finding (McMurray et al 2009)

A direct anti-inflammatory agent could, in theory, be tested at any stage of the atherothrombotic process. However, the most appropriate population to test this hypothesis is one in which (a) patients are known to be at increased risk despite current therapy, and (b) there is biochemical evidence of a persistent heightened inflammatory response despite usual

care. Recognizing these constraints, a primary prevention population would be infeasible due to the exceptionally large sample size required and because an extremely low side effect profile is typically required in that setting. In contrast, patients who have survived a MI are clinically stable, and who have persistently elevated hsCRP levels despite aggressive treatment are an optimal population in which to undertake a test of the inflammatory hypothesis of atherothrombosis. This population is no longer at risk for plaque rupture due to altered wound healing, yet remains at high risk for recurrent vascular events despite use of all accepted therapies. If alternatively designed to enroll post-MI patients without regard to hsCRP, the proposed trial would substantially lose power and would expose large numbers of individuals with already controlled inflammation to IL-1β inhibition. All of these effects would result in an adverse shift in the benefit to risk ratio as well as greatly increase study costs.

1.2 Purpose

The purpose of this trial is to test the hypothesis that canakinumab treatment of patients with MI at least one month prior to study entry and elevated hsCRP will prevent recurrent cardiovascular events. A secondary hypothesis, that canakinumab treatment in patients with MI and pre-diabetes, will prevent new onset diabetes (NOD) will also be tested. The trial is pivotal for registration for canakinumab for cardiovascular risk reduction.

2 Study objectives

2.1 Primary objective

The primary objective of this clinical trial is to demonstrate the superiority of at least one dose of canakinumab compared to placebo in reducing the risk of recurrent major cardiovascular disease events (cardiovascular death, non-fatal MI and stroke) in a population of clinically stable post-MI patients with elevated hsCRP receiving standard of care.

2.2 Secondary objectives

Key secondary efficacy objectives

- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of CV death, non-fatal MI, stroke, and hospitalization for unstable angina requiring unplanned revascularizations.
- To demonstrate superiority of canakinumab compared to placebo on the endpoint of new onset type 2 diabetes among those with pre-diabetes at randomization

Other secondary efficacy objectives

- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of all-cause mortality, non-fatal MI and stroke.
- To demonstrate superiority of canakinumab as compared to placebo on the endpoint of all-cause mortality

Safety objective

- To evaluate the long-term safety of canakinumab therapy in a placebo(standard of care) - controlled setting

2.3 Exploratory objectives

- To explore whether canakinumab compared to placebo reduces the risk of other cardiovascular disorders with a known inflammatory component:
    - Composite of deep vein thrombosis/pulmonary embolism
    - Supraventricular tachycardia/atrial fibrillation
    - Stent thrombosis (probable or definite)
    - Hospitalization or prolongation of hospitalization for heart failure
    - Cardiovascular death, non-fatal MI, stroke and all-cause mortality composite
    - Major coronary events composite (CHD death, non-fatal MI)
    - Total vascular events composite
    - Coronary revascularization procedures (PCI or coronary artery bypass graft (CABG))
    - Stroke by etiology
- To explore the dose response relationship and the effects of induction dosing in terms of cardiovascular endpoints.
- To explore whether canakinumab compared to placebo reduces nephropathy as assessed by albumin/creatinine ratio in patients with T2DM or pre-diabetes at randomization
- To explore whether canakinumab compared to placebo improves glycemic control among those with type 2 diabetes
- To explore whether canakinumab compared to placebo affects biomarkers of cardiovascular and diabetes risk, including inflammatory biomarkers, glycemic control markers, β-cell function markers
- To explore whether canakinumab as compared to placebo affects patient reported outcomes of tiredness, physical function and performance function and improves health status as assessed by the EQ-5D Quality of Life (QOL) assessment.
- To perform exploratory pharmacogenetic and pharmacogenomic assessments to examine whether individual genetic variation in genes relating to drug metabolism, major cardiovascular events, type 2 diabetes, and the drug target pathway confer differential response to canakinumab.

3 Investigational plan

3.1 Study design

This study is a Phase 3, multi-center, randomized, parallel group, placebo-controlled, double-blind event-driven global clinical trial. The study is designed to evaluate the benefit of a quarterly dose of 150 mg canakinumab and an induction followed by quarterly dose of 300

mg canakinumab subcutaneously compared to placebo in stable post-MI patients receiving standard of care therapy who have been selected by an elevated inflammatory burden as determined by hsCRP ≥ 2 mg/L. The index qualifying MI must have occurred at least 30 days prior to randomization. There is no upper limit for post- MI for inclusion into the study. Standard of care post-MI background therapy includes but is not limited to appropriate lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as defined by local guidelines. Patients should also be instructed to follow heart healthy (low fat) diet and regular exercise program.

Pre-Screening: Pre-screening is a key element to successfully identifying the correct patients to be screened for this clinical study. All patients should have an available hsCRP value prior to the time of screening. The available hsCRP value should be at least 28 days after a cardiovascular event or procedure or major surgical procedure, and must be less than 60 calendar days prior to screening. The Pre-screening visit should be used after review of the patient's charts to determine patient's eligibility and to obtain an hsCRP value, which is to be run locally, for those potentially eligible patients who do not have one available.

Screening: Screening will take place no earlier than:

- 28 days after the index MI and on stable long term medication.
- 28 days after a PCI if it was during a different hospital admission than the qualifying MI. Screening can only be initiated following this procedure.
- 3 years post a CABG procedure regardless of timing of the qualifying MI.

All screened patients must be called into the IVRS. Screening evaluations will include hsCRP and determination of tuberculosis status among other measurements and procedures. After screening visit, patients may be randomized, as soon as, results from screening laboratory and other studies are available. However, this can be no earlier than 30 days after the index MI.

The time between screening and randomization should be approximately 4 weeks. Patients may be randomized as soon as eligibility assessments have been completed. Generally rescreening is not allowed. However, patients may be re-evaluated as noted in the inclusion and exclusion sections (only applicable for out of range systolic and diastolic blood pressure). Patients re-evaluated will retain their screening number and be randomized or screen failed based upon the result of the re-evaluation.

Randomization will be stratified by time since most recent index myocardial infarction with 50% of the population in each stratum (30 days to <6 months and ≥6 months). Patients should be hemodynamically stable at the time of randomization. The Steering Committee and Sponsor will monitor the patient profiles during recruitment phase and may increase or restrict enrollment of certain sub-groups of patients to avoid imbalances. There will be no upper limit for post MI for inclusion into the trial. Once randomized, patients will return to the clinic for scheduled visits as shown in the study assessment schedule. Some assessments at these visits will include physical examinations, vital sign measurements, electrocardiogram (ECG) , instruction on how to follow a heart healthy (low fat) diet and regular exercise program and clinical laboratory measurements including glucose control, lipids, biomarkers, and routine safety assessments..

Patients will have scheduled assessments at months 0.5, 1.5, and 3 after randomization and quarterly visits thereafter to evaluate safety and the occurrence of any trial endpoints, as well as, to receive scheduled (excluding month 1.5) subcutaneous injections of active therapy and/ or placebo. Genetic blood samples and biomarker samples collected at randomization, month 3, one year and end of study (EOS) visit will be shipped to the Central Laboratory for long term storage. Upon completion of the study, these samples will be analyzed for cardiovascular and metabolic biomarkers and genetic analysis, if prior written informed consent is obtained.

The trial is event driven and designed to complete when a total of 694 patients have experienced a primary cardiovascular endpoint. Double blind treatment will be continued until the target number of primary cardiovascular endpoints has been reached. Sites will then be notified to have all patients return to complete an EOS visit. The elapsed calendar time to reach conclusion of the study is estimated to be a total of 4.5 years of treatment and follow-up from the start of enrollment in the trial to the occurrence of 694 confirmed cardiovascular events. These estimates are based on the assumption that the time necessary to complete enrollment in the study will be approximately 18 months.

Following a successful completion of this trial all patients who are either normoglycemic or have T2DM will be enrolled in an open label follow-up study where participants will be treated with canakinumab in order to determine long term safety and efficacy of canakinumab treatment. Patients with pre-diabetes at the end of this trial (based on the last available HbA1c 5.7-6.4 or FPG 100-125 mg/dL) will first enter into the 6 month washout phase followed by the open label follow-up study including re-starting canakinumab treatment. This safety follow-up study will collect safety events to be determined based on canakinumab profile in the main trial and major cardiovascular adverse events (AE) as defined in the primary endpoint of the main trial at bi-annual visits. An extension protocol with detailed study information including length of the follow-up will be developed for the open label follow-up study.

Patients who discontinue study treatment

Every attempt to determine follow-up status of patients who discontinue study treatment, for a*ny* reason prior to the completion of the trial, must be made unless prohibited by local regulations. It is required that these patients are contacted at least 3 months post last dose of medication; and then as per study schedule to ensure all endpoints (safety and efficacy) are collected and reported. It will be at the discretion of the site staff to determine if these patients will be contacted by phone or attend the regularly scheduled visits.

Any patient who stops study treatment, withdrawals consent (if re-consented) or becomes no longer lost to follow up, is allowed to re-start the study treatment at the discretion of the investigator regardless of length of time off study treatment.

End of Study Follow-up for all pre-diabetic patients

Once all study endpoints have been reached and the site staff is contacted to have all patients return for their EOS visit, any patient with a pre-diabetic status (based on the last available laboratory results) will enter into an additional 6 month washout follow-up period without study treatment. At the end of this period, new onset diabetes endpoint measurement using HbA1c will be repeated. The purpose of this washout period is to assess to what extent a lower incidence of diabetes diagnoses observed between canakinumab and placebo during double-blind treatment is explained by a true delay in progression to diabetes as opposed to a lowering of FPG and HbA1c that masks diabetes but does not persist after the washout period.

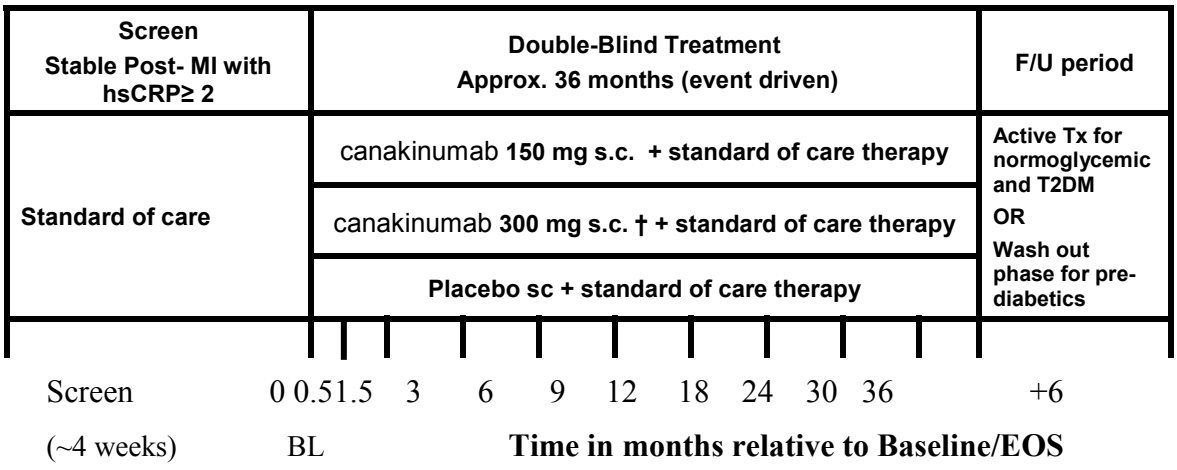
Sub-Studies

All patients who suffer a stroke during the double-blind period will participate in the, Post-Stroke Functional Assessment Sub-Study; see Section 6.6.4 for further details.

Interim Analysis

Interim analyses will be conducted for this trial; please Sections 3.5 & 9.8 for details.

Figure 3-1 Study design



Months 15, 21, 27 & 33 are drug dispensing visits only and therefore not displayed.

†- canakinumab 300 mg s.c. induction at randomization (month 0) and week 2 (month 0.5), and then 300 mg s.c. quarterly beginning at week 12.

3.2 Rationale of study design

This study has been designed as a multi-center, randomized, parallel group, placebo-controlled, double-blind, event-driven trial to provide definitive evidence on the effects of canakinumab on cardiovascular adverse events in patients with recent MI and elevated inflammatory burden as evidenced by elevated hsCRP. This study will also measure the effects of canakinumab on the conversion to NOD as a secondary endpoint. This study design is the most robust clinical trial design to test the hypothesis that anti-inflammatory treatment with canakinumab will reduce major adverse cardiovascular events.

3.3 Rationale of dose/regimen, duration of treatment

In phase II studies in patients with gout, diabetes, and acute inflammatory conditions, safety of canakinumab across a wide range of doses has not emerged as a major clinical issue. Due to long term suppression of inflammatory biomarkers, quarterly dosing of canakinumab is feasible and likely to be clinically effective. In addition, data in the setting of acute inflammation suggests that higher initial doses of canakinumab that can be achieved through induction are safe and provide an opportunity to ameliorate concern regarding potential auto-induction of IL-1β and to achieve greater early suppression of IL-1β related gene expression. IL-1β auto-induction has been shown in human mononuclear blood, human vascular endothelial, and vascular smooth muscle cells in vitro and in rabbits in vivo where IL-1 has been shown to induce its own gene expression and circulating IL-1β level (Dinarello et al. 1987, Warner et al. 1987a, and Warner et al. 1987b). These studies suggested that IL-1 induced IL-1 gene expression may provide a positive feedback mechanism in the pathogenesis of atherosclerosis and promote atherosclerosis. This consequently suggests that suppression of this feedback mechanism may provide benefits in the atherosclerotic lesion. Specifically, data supporting an induction dose of canakinumab includes the following: In CACZ885A2102, a

CAPS mechanism of action study of patients with Muckle Wells Syndrome (N=4), canakinumab treatment with 10 mg/kg i.v. (equivalent to 600 mg i.v.) single dose induced clinical (improved skin lesions and conjuctival injection) and biomarker (hsCRP and SAA) responses in 24 hrs which was durable up to 180 days. In contrast, canakinumab doses of 1 mg/kg i.v. without induction were only durable up to 90 days. Support for more sustained and higher dose canakinumab therapy was also seen in the rheumatoid arthritis proof of concept study CACZ885A2101, where higher doses of canakinumab were required ($\geq$ 3.0 mg/kg i.v.) to achieve a significant clinical response as scored by the ACR system. Furthermore, in the CACZ885A2102 study, analysis of gene expression known to be related to IL-1 β expression, inflammasome activity, and autoinduction of IL-1 β, showed more complete response to higher dose (10 mg/kg i.v.) than lower dose (1 mg/kg i.v.) canakinumab. In addition, IL-1β and inflammasome related gene expression modification began to decrease with the lower dose (1 mg/kg i.v.) compared to the higher dose (10 mg/kg i.v.) between 10 and 12 weeks. Similar results were obtained in the rheumatoid arthritis study CACZ885A2201 where IL-1β related genes were suppressed more with 300 mg s.c. q2weeks dosing than 150 mg q4weeks dosing.

Thus, the CACZ885M2301 trial regimens will consist of (a) placebo s.c. at randomization (month 0), placebo s.c. at week 2 (month 0.5), placebo s.c. at week 12 (month 3), and then placebo s.c. quarterly; (b) canakinumab 150 mg s.c. at randomization (month 0), placebo s.c. at week 2 (month 0.5), canakinumab 150 mg s.c. at week 12 (month 3), and then canakinumab 150 mg s.c. quarterly; and (c) canakinumab 300 mg s.c. at randomization (month 0), canakinumab 300 mg s.c. at week 2 (month 0.5), canakinumab 300 mg s.c. at week 12 (month 3), and then canakinumab 300 mg s.c. quarterly.

Canakinumab 150 mg quarterly

The 150 mg canakinumab dosing schedule has been selected on the basis of anticipated efficacy, safety, and biomarker modeling data. In phase II development, all canakinumab doses up to 300 mg s.c. every other week have been found safe, well tolerated, and free of adverse lipid effects. The optimal dosing interval was examined using data from CACZ885A2213 (diabetes) and from gout studies with canakinumab data on file. These studies indicated that canakinumab effect on lowering hsCRP was durable for up to approximately 3 months. Further, modeling and simulation methods showed that 150 mg quarterly dosing had similar free IL-1β suppression compared to 50 mg monthly dosing. This conclusion was reached by comparing the doses and regimens based on both the time for maintenance of suppression and the fraction of patients below a specified suppression threshold of 'tissue free' IL-1β. Canakinumab efficacy in lowering hsCRP, IL-6 and fibrinogen was assessed based on studies CACZ885A2213 and CACZ885I2202. The maximum efficacy of hsCRP lowering in study CACZ885I2202 was at approximately 50 - 75 mg of canakinumab monthly, with persistent lowering across a wide range of higher doses. Therefore, canakinumab 150 mg quarterly administration was selected for the lower, conventionally efficacious dose in this study, CACZ885M2301.

Canakinumab 300 mg quarterly

Given evidence of safety across a wide dosing range, a 300 mg quarterly dosing schedule for canakinumab has also been developed for CACZ885M2301. This allows evaluation of a

higher canakinumab dose since the dose needed for adequate IL-1β neutralization within the plaque or systemically in inflammation-based atherosclerosis is not established. Therefore, a higher dose may deliver greater efficacy than the other selected dose, 150 mg quarterly. This 300 mg quarterly dosing regimen also includes an induction period over 2 weeks, dosing at randomization (month 0) and at week 2 (month 0.5), in order to assure that auto-induction of IL-1β pathway is adequately inhibited at study initiation. The complete suppression of IL-1β related gene expression achieved with this early high dose administration, coupled with the continuous canakinumab treatment effect which has been proven to last the entire quarterly dosing period, is expected to minimize the potential for IL-1β rebound. This may be relevant for pathogenesis of atherosclerosis because it is theorized that IL-1 auto-induction provides a positive feedback mechanism for vascular disease including atherosclerosis. The lower 150 mg quarterly dose does not include an early high, induction dose regimen to ensure separation of the two canakinumab dose levels included in this protocol and to allow assessment of the impact of the early high dose regimen included in the 300 mg arm on clinical cardiovascular events.

The documented safety record of canakinumab up to doses of 300 mg s.c. every 2 weeks with and without induction dose of 600 mg i.v., study CACZ885A2201 in rheumatoid arthritis patients up to 6 months, 300 mg q1month, study CACZ885H2257 in gout patients up to 6 months, and 150 mg q1month, study CACZ885I2202 in T2DM patients up to 4 months supports the use of this higher dose regimen.

3.4 Rationale for choice of comparator

This trial is placebo controlled to provide robust evidence on the effects of canakinumab on clinical events and safety as well tolerability. No comparative anti-inflammatory treatment has been shown to date to benefit patients with cardiovascular disease and thus an active comparator arm is not available. All patients in all treatment arms will receive standard of care post-MI background therapy including, but not limited to, lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as appropriate. High dose statin comparator therapy was initially considered as an appropriate active comparator; however, it was felt that it would be unethical to restrict use of proven benefit high dose statin therapy to the comparator arm only.

3.5 Purpose and timing of interim analyses/design adaptations

Interim analyses (IA) of efficacy, futility and safety will be carried out during the study in order to avoid exposing study patients to ineffective treatment or undue risks or to allow study discontinuation in case of overwhelming efficacy. Two interim analyses of efficacy will be performed when approximately 50% of the target number of patients with primary endpoints have been accumulated and the second one when approximately 75% of the planned number of patients with primary endpoints are available.

Interim analyses for futility will be conducted simultaneously with the analyses of efficacy. The criteria for formal statistical significance at the interim analyses are specified in the data analysis section of the protocol, but details on futility boundaries and stopping rules will be pre-specified in the charter of the Data Monitoring Committee (DMC). The timing and

number of safety analyses will also be specified in DMC charter, but these are estimated to occur on a six-month basis.

The unblinded results of the interim analyses will be reviewed by the DMC. Investigators, Novartis, and others who are involved in the conduct of the trial, in the analysis of the final trial results, or who have contact with study centers, will remain blinded to the treatment codes and interim analysis results until all monitoring decisions have been made and the database has been locked for final analysis.

4 Population

Participants eligible for this trial will include male and non-child-bearing potential female patients age 18 years and older who (a) have suffered a documented acute myocardial infarction at least 30 days before randomization and (b) have persistent evidence of systemic inflammation on the basis of an hsCRP $\geq$ 2 mg/L despite the use of standard of care post-MI medical therapies. Standard of care post-MI background therapy includes, but is not limited to, lipid lowering, anti-hypertensive, beta blockers, and anti-platelet therapy as appropriate.

In data from the PROVE IT – TIMI 22 trial, 43 percent of a post-MI population screened at 30 days had hsCRP $\geq$2 mg/L despite maximal therapy including high-dose statin (Ridker et al 2005).

In previous registries and studies of post-MI patients, approximately 25 percent are likely to have a diagnosis of T2DM, 35 percent are likely to be pre-diabetic, and 40 percent are likely to be normoglycemic patients. In this trial the following definitions of pre-diabetes and type 2 diabetes at randomizations will be used:

Definition of randomization Pre-Diabetes

- At visit 1 OR 2 HbA1c of 5.7-6.4% or FPG 100-125 mg/dL (ADA 2010 Clinical Practice Recommendations)

Definition of randomization Type 2 Diabetes

- At Visit 1 (screening) and Visit 2 (Randomization/Baseline) any patient with:
  - Medical history of type 2 diabetes and any patient currently on concomitant anti-diabetic medication

    or
  - HbA1c $\geq$6.5% (visit 1 and visit 2)

    or
  - FPG $\geq$ 126 mg/dL (visit 1 and visit 2).

    or
  - Combination of FPG $\geq$ 126 mg/dL and HbA1c $\geq$6.5% (visit 1 and visit 2)

The trial will be an event-driven global trial conducted in the outpatient setting. It is anticipated that approximately 694 cardiovascular endpoints will accrue during the course of the trial (see Section 9.7 for Power Calculations). To accomplish this goal, it is expected that

around 14,600 patients will need to be screened in order to randomize approximately 7,302 patients.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male, or Female of non-child-bearing potential
3. Age ≥ 18 years at Visit 1.
4. Documented spontaneous MI (diagnosed according to the universal MI criteria with or without evidence of ST segment elevation) at least 30 days before randomization. (Thygesen et al 2007)
   - Diagnosis of prior MI should be based on medical history of clinical symptoms consistent with myocardial ischemia associated with elevation of cardiac biomarkers above the 99th percentile of the upper reference limit (preferably troponin) OR development of new pathological Q waves regardless of symptoms (see Appendix 3: ECG changes associated with prior myocardial infarction (Thygesen et al 2007). For details, refer to the Universal Definition of MI (Thygesen et al 2007). Patients with MI resulting from PCI or CABG will not be eligible
5. Have an hsCRP ≥ 2 mg/L at screening (Visit 1) (which is at minimum of 28 days after qualifying MI or after any PCI performed separately from qualifying MI) on stable (at least 4 weeks) long term medications.

4.2 Exclusion criteria

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/ml)
2. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are
   a. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml (for US only***:*** and estradiol < 20pg/ml) or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
3. Any of the following concomitant conditions or diseases:
   a. Planned coronary revascularization (PCI or CABG) or any other major surgical procedure.
   b. Major non-cardiac surgical or endoscopic procedure within past 6 months to Visit 1
   c. Multi-vessel CABG surgery within the past 3 years
   d. Symptomatic patients with Class IV heart failure (HF) (New York Heart Association [NYHA].

e. Uncontrolled hypertension (defined as an average SBP >160 mmHg or an average diastolic blood pressure (DBP) >100 mmHg at Visit 1. Patients are allowed to be re-evaluated, at the discretion of investigator for this criterion if anti-hypertensive therapy has been started or increased as a result of initial screening blood pressure above these limits. (Mancia et al 2009).

f. Uncontrolled diabetes as defined by the investigator

g. Nephrotic syndrome or eGFR < 30 mL/min/1.73 m^2 per MDRD formula or kidney transplant (regardless of renal function), at Visit 1

h. Known active or recurrent hepatic disorder (including cirrhosis, hepatitis B and hepatitis C, or alanine aminotransferase/ aspartate aminotransferase (ALT/AST) levels > 3 times ULN or total bilirubin > 2 times ULN) ,Visit 1

i. Prior malignancy other than basal cell skin carcinoma

4. A history of alcohol and/or substance abuse that could interfere with the conduct of the trial

5. History or evidence of active tuberculosis (TB) infection at Visit 1 or one of the risk factors for tuberculosis such as but not limited or exclusive to:

   a. History of any of the following: residence in a congregate setting (e.g. jail or prison, homeless shelter, or chronic care facility), substance abuse (e.g. injection or non-injection) health-care workers with unprotected exposure to patients who are at high risk of TB or patients with TB disease before the identification and correct airborne precautions of the patient

      or

   b. Close contact (i.e. share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours)) with a person with active pulmonary TB disease within the last 12 months.

6. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection, at Visit 1, determined as defined by local guidelines/ local medical practice (see also below for determination of tuberculosis status). If presence of tuberculosis is established then treatment (according to local guidelines) must have been completed prior to randomization.

7. Patients with suspected or proven immunocompromised state, including (a) those with evidence of Human Immunodeficiency Virus (HIV) infection; Patients on anti-retroviral therapy are excluded (b) those with any other medical condition which in the opinion of the investigator places the patient at unacceptable risk for participation in immunomodulatory therapy; or (c) those requiring systemic or local treatment with any immune modulating agent in doses with systemic effects e.g. high dose oral steroids. Topical, inhaled, local steroid use in doses that are not considered to cause systemic effects are permitted.

8. Live vaccinations within 3 months prior to the randomization visit or live vaccinations planned during the trial.

9. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.

10. Patients who have received an investigational drug or device within 30 days (inclusive) of Visit 1, or who are expected to participate in any other investigational drug or device study during the conduct of this trial, except for patients who have an investigational treatment eluting stent (DES), provided that they have completed the DES trial. FDA/country-specific drug regulatory authority approved DES devices are permitted.
11. Any biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, tocilizumab)
12. Any life threatening condition with life expectancy < 5 years, other then vascular disease that might prevent the patient from completing the study

Determination of tuberculosis status

Determination of tuberculosis status will be required before administration of study drug and should be performed as defined by local guidelines. Patients need to have given written informed consent before any of these assessments are initiated. Patients who have had any one of the below assessments performed within 30 days of screening, Visit 1, will not need repeat testing performed to determine eligibility. All other patients will need tuberculosis status determined at Visit 1. .

Any significant findings will be recorded in the "Medical History" section of the eCRF as necessary

Patients with either a positive PPD or QFT-g test may still participate in the study if

1. Treatment (according to local guidelines) has been completed prior to randomization

or

2. Further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis.

PPD skin test

A PPD skin test may be initiated to evaluate for an occult infection with TB. The test dose is bioequivalent to 5 tuberculin units (or as according to local standard practice) of standard PPD usually injected intradermally into the volar surface of the forearm. The injection site will be cleansed and the PPD extract will then be injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

A reaction will be measured in millimeters of indurations (hard swelling) after 48h – 72h. A PPD skin induration > 5 mm is interpreted as positive result. This will determine whether the patients have had a significant reaction to the PPD skin test.

The investigator will either obtain PPD skin tests on his own and be reimbursed by Novartis for its cost or be supplied with them by the Novartis affiliate, depending on the local Novartis policy.

QuantiFERON-TB Gold assay

A QuantiFERON®-TB Gold assay may be performed to assess the TB status at baseline on patients as needed.

This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin vaccination or exposure to other Mycobacteria species. This test, in contrast to the PPD skin test, is also insensitive to a booster effect since the patient is not exposed to the vaccine. The assay measures the production of interferon-gamma and puts it into relation to a negative and a positive control sample.

QuantiFERON®-TB Gold samples will be processed by the central lab.

Details about sample processing are described in the central laboratory manual.

Chest x-ray

A chest x-ray may be performed if required by local regulations in case of positive PPD skin test or QuantiFERON-TB Gold® assay.

If in line with local guidelines/ local medical practice, a chest x-ray only will be sufficient to check eligibility with respect to TB status prior to randomization. This x-ray should be no more than 30 days old at the time of screening.

5 Treatment

5.1 Investigational and control treatment

Canakinumab (ACZ885) or matching placebo solution for injection will be provided by Novartis as ready-to-use pre-filled syringes. The sites will receive their first shipment of study treatment only after the first screened patient has been registered in the IVRS/IWRS. One strength will be supplied: Canakinumab 150 mg in 1 mL solution for injection, as well as, one placebo formulation matching to the active drug formulation. The study drug will be given as subcutaneous injections at randomization, week 2 (month 0.5), and then quarterly beginning at week 12 (month 3). All injections (double dummy design, two syringes of 1 mL) will be administered at study sites by trained site staff, facilitating both compliance and long-term follow-up for both safety and efficacy outcomes. Please see Table 5-1 below for planned canakinumab injections at study visits. Study treatment and/or placebo will be given in addition to local standards of care for post-MI patients which may include lipid lowering, anti-hypertensive, beta blockers and anti-platelet therapies and is determined by the responsible treating physician. The sites should make alternative arrangements for those patients likely to miss visits due to travel or other reasons to be seen in an alternative study site.

No study treatment will be provided for those pre-diabetic patients at their final visit and during the 6 month washout period.

Table 5-1 Injection Description

Treatment Groups	Injections at all visits excluding Screening, month 0.5 and 1.5 visits	Injections at Visit month 0.5
Canakinumab 150 mg sc	1 x canakinumab 150 mg and 1 x matching placebo	2 x placebo matching canakinumab 150 mg
Canakinumab 300 mg sc	2 x canakinumab 150 mg	2 x canakinumab 150 mg
Placebo	2 x placebo matching canakinumab 150 mg	2 x placebo matching canakinumab 150 mg

5.2 Treatment arms

Patients will be assigned to one of the following 3 treatment arms in a ratio of 1:1:1

- Canakinumab 150 mg s.c. at randomization (month 0), placebo s.c. at week 2 (month 0.5) , 150 mg s.c. at week 12 (month 3) and thereafter 150 mg s.c. quarterly
- Canakinumab 300 mg s.c. at randomization (month 0), week 2 (month 0.5) , week 12 (month 3) and thereafter 300 mg s.c. quarterly
- Placebo s.c. at randomization (month 0), week 2 (month 0.5) , week 12 (month 3) and thereafter placebo s.c. quarterly

5.3 Treatment assignment

At Visit 2, all eligible patients will be randomized via Interactive Voice Response System /Web System (IVRS/IWRS) to one of the treatment arms. The investigator or his/her delegate will contact the IVRS/IWRS after confirming that the patient fulfills all the inclusion/exclusion criteria. The IVRS/IWRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IVRS/IWRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to study drug packs containing each of the study treatment.

Stratification

Randomization will be stratified by 'time since most recent MI' as follows:

- 50% Post MI $\geq$ 30 days but < 6 months
- 50% Post MI $\geq$6 months

Sites will be asked to indicate the patients' glycemic status at the first call post randomization as the V2 lab results are needed for the following categories (see Section 3.1 for definitions):

- Normoglycemia: HbA1c <5.7% at V1 and V2
- Pre-Diabetes: HbA1c 5.7 – 6.4 % or FPG 100-125 mg/dL inclusive at V1 or V2
- T2DM: (patient needs to have one or more of the following)
  - HbA1c ≥ 6.5% OR FPG ≥ 126 mg/dL at V1 and V2
  - Combination of HbA1c ≥ 6.5% and FPG ≥ 126 mg/dL as confirmed at V1 and V2
  - Medical history of T2DM and on a current anti-diabetic medication

Sites are required to call the IVRS at every visit to:

- Visit 1: Register the screening visit. The first shipment of study treatment will ONLY be sent once the site registers their first screened patient.
- Visit 2: Register Screen Failures or randomize a patient
- Visit 3: Register the occurrence of the visit
- Obtain medication numbers for randomization (month 0), week 2 (month 0.5), week 12 (month 3), and quarterly dispensing of study treatment thereafter
- Register a patient who has died or withdrawn consent
- Register a patient who has completed (this will only occur when the study has been deemed complete by the DMC or Novartis and the patient returns for the EOS visit.)

The randomization scheme for patients will be reviewed and approved by a member of the IIS

Biostatistics Quality Assurance Group. The randomization codes will be maintained at Center for Cardiovascular Disease Prevention, Brigham and Woman's Hospital, Harvard Medical School.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of the independent unblinded statistician, programmer and data manager/data coordinator (and assistant as required), who need to have access to prepare safety and efficacy interim analysis reports for the DMC. These personnel will not be involved in any other trial activities.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration and appearance.

The first two study medication injections received for the open label safety follow up study (at the main study EOS visit) will be blinded in order to keep blinding intact during study closeout phase and database lock

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9) at the time of interim analysis and at the conclusion of the study. In the event a patient becomes

unblinded for any reason they may continue study treatment and assessments according to the protocol at the discretion of the investigator.

PK, biomarkers, immunological laboratory and canakinumab antibody results will be blinded to the sites and Novartis but will be available unblinded for the DMC analyses to assure patient safety.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a **Patient Number**. A center number is also assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned the next sequential patient number by the investigator. The investigator or his/her staff will contact the IVRS/IWRS and provide the requested identifying information for the patient to register them into the IVRS/IWRS. In the electronic data capture (EDC) system, there will be blank CRF books available labeled with a Patient Number. The site should select the CRF book with a matching Patient Number to enter data.

Once assigned to a patient, the Patient Number will not be reused. If the patient fails to be randomized for any reason, the IVRS/IWRS should be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Period Phase Disposition eCRF.

5.5.2 Dispensing the study treatment

Each study site will be supplied by Novartis with study treatment in packaging of identical appearance. The first shipment of study treatment will occur once the site has registered their first screened patient in the IVRS/IWRS. All injections should be administered by the site staff only.

The study treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the 2 formulations provided (one active and one placebo forms). Investigator staff will identify the two study treatment packages for the patient at each dispensing visit by contacting the IVRS/ IWRS and obtaining the medication numbers. Immediately before administering the study treatment, the, investigator staff will detach the outer parts of the labels from the packaging and affix them to the source document (Drug Label Form) for that patient's unique patient number.

5.5.3 Supply, storage and tracking of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, all study treatment should be stored in the refrigerator according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and no information about the patient.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability ledger. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

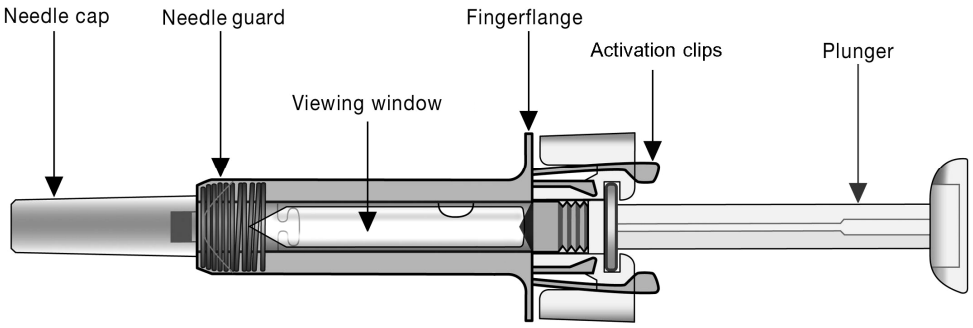
5.5.4 Instructions for prescribing and taking study treatment

Canakinumab syringe

Before using the syringe, please read the following information carefully.

The pre-filled syringes are individually sealed in a plastic tray.

Parts of the pre-filled syringe



Important Safety Information

1. Be careful not to touch the device activation clips (see illustration above) at any time. By touching them, the safety device may self-activate.
2. Do not remove the needle cap until just before you give the injection.
3. The syringe cannot be re-used. Dispose of the used syringe immediately after use into a sharps container.

Storage of the pre-filled syringe

1. Store the syringe in a refrigerator, sealed in its plastic tray according to the labeled storage condition.
2. Do not use the syringe after the expiration date shown on the outer box or syringe label.

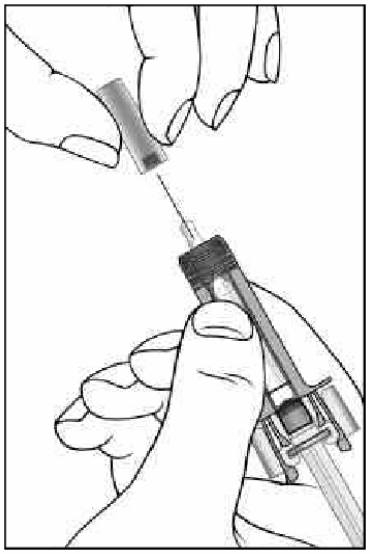
Preparing the syringe for use

Warning: Prior to completion of the injection, avoid contact with the device activation clips (see first illustration) to keep it from prematurely covering the needle with the needle guard.

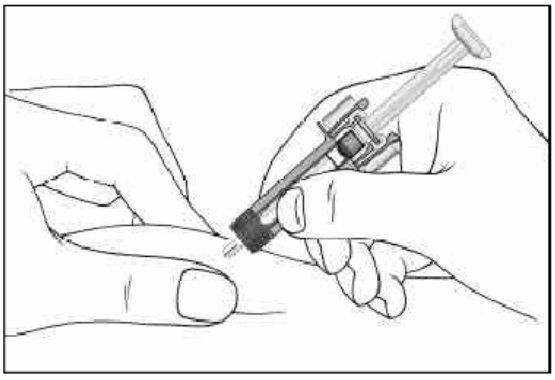
1. Remove the plastic tray containing the syringe from the refrigerator. Do not uncover the plastic tray.
2. Allow the tray to come to room temperature (approximately 20 minutes)
3. Peel back the paper cover from the plastic tray, and remove the syringe.
4. Inspect the syringe. DO NOT USE if it is broken or if the liquid looks cloudy or contains particles. The air bubble in the syringe is normal. You do not have to expel any air before use.

How to use the syringe

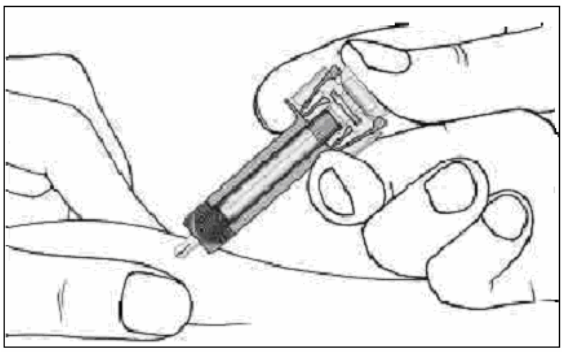
Step 1: Hold the syringe vertically with the needle cap up and carefully remove the needle cap from the syringe. Discard the needle cap. Do not touch the needle after the cap is removed.



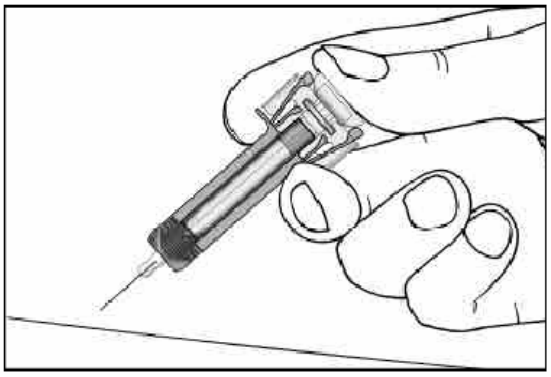
Step 2: Gently pinch the skin at the injection site. Insert the needle.



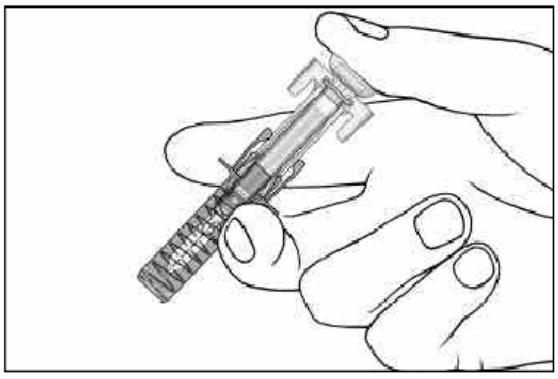
Step 3: Holding onto the finger flange, slowly press the plunger all the way down until all the drug is injected.



Step 4: After the complete dose is given, hold the syringe in place for 5 seconds to allow the drug to distribute in the tissue. Then, by holding the plunger down, remove the needle from the skin.



Step 5: Slowly release the plunger and allow the needle guard to automatically cover the exposed needle.



NOTE: If the needle guard does not extend automatically, firmly push on the plunger. Then release the plunger and allow the guard to cover the needle.

Step 6: Dispose the used syringe immediately into a sharps container.

All randomized patients will receive two subcutaneous injections per visit, beginning at randomization (month 0), week 2 (month 0.5) and then quarterly beginning at week 12 (month 3).

Patients will receive either one injection of canakinumab and one injection of placebo, or two injections of placebo or two injections of canakinumab. Injections will be given after all other study assessments have been completed for the visit. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF. All drug kits assigned by the IVRS/IWRS will be recorded/databased in the IVRS/IWRS. The investigator should promote compliance by informing the patient that compliance is necessary for the patient's safety and the validity of the study.

Principal investigator or trained staff will select injection site(s) for the study injections, which may be administered subcutaneously in the abdomen and/or extremities.

5.5.5 Permitted dose adjustments and interruptions of study treatment

For patients who are unable to tolerate the protocol-specified dosing scheme, dose interruptions are permitted in order to keep the patient on study treatment. Patients are encouraged to continue study treatment; however, patients are allowed to interrupt and re-start medication at any time during the study at the discretion of the investigator.

These changes must be recorded on the Dosage Administration Record CRF (eCRF).

5.5.6 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after signing the informed consent. All medications and significant non-drug therapies (including physical therapy and blood transfusions) taken within 30 days of screening and administered after the patient has signed informed consent must be listed on the appropriate Concomitant Medications and or Procedures and Significant Non-Drug Therapies eCRF.

Patients who are on warfarin or warfarin like treatment with narrow therapeutic index should have their international normalized ratio (INR) measured locally and warfarin or warfarin like treatment dose adjusted accordingly within one month from starting study treatment. This is a general precautionary measure because canakinumab is not expected to interact with warfarin.

5.5.7 Prohibited treatment

Use of any treatments below are NOT allowed after the start of study treatment due to potential increase in immunosuppressant related concomitant conditions. They are prohibited for the duration of the study and for at least 90 days after discontinuation of study treatment.

If a patient chooses to continue one of the medications below, they would still be required to be followed as per protocol to assess for any potential study endpoints. If a patient stops taking any of the below prohibited medications they are eligible to restart study treatment 90 days after stopping the prohibited medication, at the discretion of the investigator.

- Any anti retro-virals and / or any biologic drugs targeting the immune system (e.g., TNFα blockers, anakinra, rituximab, abatacept, tocilizumab)
- immune suppressive drugs :e.g. high dose systemic oral steroids

5.5.8 Discontinuation of study treatment and premature patient withdrawal

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation of study treatment would be detrimental to the patient's well-being. If any patient discontinues study treatment, the site is required to follow the patient, as per the study assessment schedule (either by phone or on site visits) until the site has been notified by Novartis that the study has been deemed complete.

Study treatment *must* be discontinued under the following circumstances;

- Withdrawal of informed consent. Study treatment may only be resumed if the patient has re-consented to participation
- Pregnancy, patient must discontinue study treatment if pregnant; however, they can resume participation in the study after stopping breast feeding.
- Use of prohibited treatment as per Section 5.5.7
- Any other protocol deviation that results in a significant risk to the patient's safety

Any of the following laboratory abnormalities

Clinical Symptoms as noted below, without regard to Liver Function Test's (LFT)

- A jaundice like event
- Any serious adverse event (SAE) indicative of fatal or non fatal hepatitis, liver failure or its complications

LFT elevations and Clinical Symptoms

- ALT or AST > 3X ULN
- Clinical symptoms suggestive of hepatic dysfunction – such as general malaise, fatigue, abdominal pain, nausea, vomiting or rash with eosinophilia

Asymptomatic elevations of ALT / AST /T. Bilirubin

- ALT or AST > 3x ULN with a T. Bilirubin > = 2x ULN

Asymptomatic isolation of elevations of ALT or AST

- ALT or AST > 8 x ULN discontinue study treatment if elevation persists > 48 hrs
- ALT or AST ≥ 5x ULN ≤8x ULN discontinue study treatment if elevation persists > 2wks.
- ALT or AST≥ 3x ULN <5 ULN discontinue medication at the discretion of the investigator

Asymptomatic isolation elevation of T. Bilirubin

- T. Bilirubin ≥ 3x ULN discontinue if elevation persists > 2 wks

Study treatment may be restarted at the discretion of the investigator, if the reason for withdrawal of study treatment has resolved. Every effort should be made to restart study treatment, if deemed appropriate by the investigator(s)

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Patient Status

Patients may voluntarily withdraw from the study for any reason at any time; however, they must be reminded that the site will attempt to obtain a vital status yearly and at the conclusion of the trial to assess for any potential study endpoints.

Study Treatment Discontinuation: If premature discontinuation of study treatment occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature discontinuation from treatment. Patients who discontinue study treatment should NOT be considered withdrawn from the study. For any patient who chooses to discontinue study treatment, the site must capture this information on the Drug Accountability Record eCRF. The site must contact the patient as per the assessment schedule as every effort must be made by sites staff to follow patients for cardiovascular events and health status. It is at the discretion of the investigator if the patient is to return to the clinic for regular visits or be contacted by telephone. If at the end of study, contact is made to the patient (or on site visit) to assess a health status; the patient will be deemed "completed".

Lost to-Follow-up: Sites must make every effort to reach patients who fail to return for visits, or become lost to follow-up for any reason, as all patients must be accounted for, at the EOS, to assess for study endpoints. The investigator must show "due diligence" by documenting in the source documents the steps taken to contact patients who are lost to follow-up (i.e. those patients whose life or death status is unclear because they fail to appear for study visits without stating an intention to withdraw). Steps taken include dates of telephone calls, registered letter confirmations, and etc. Sites will be requested to complete the Visit Information eCRF at the regularly scheduled study time points to document the attempts made to contact a person. "Lost to Follow Up information will be captured on the Study Phase Completion eCRF only if sites are unable to obtain a status on a patient at the end of the study. It is permissible for a patient to contact the site to return for a scheduled clinic visit, at which time their status should then be updated in the systems appropriately. Patient will maintain the previously provided Patient Number and resume study activities based upon their original randomization date.

Withdraw Consent: Any patient who withdraws their consent to participation of study procedures will have this information captured on the Study Phase Completion eCRF, which will prompt annual completion of the Survival Information eCRF. To complete the Survival Information page; sites will be asked to check public registries on an annual basis to try and obtain a health status on their patients. Patients may re-consent at any time to resume their participation in the trial. Patients will maintain the previously provided Patient Number and resume study activities based upon their original randomization date.

Patients who discontinue study treatment prematurely will not be replaced by an equal number of newly enrolled patients.

5.5.9 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IVRS/IWRS. When

the investigator contacts the system to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Head that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IVRS/IWRS in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study treatment name if available, patient number, and instructions for contacting the local Novartis Country Pharma Organization (CPO) (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable.

Any patient who is unblinded will continue in the study and may continue medication as per protocol.

5.5.10 Study completion and post-study treatment

The study closeout will be initiated once the study has reached its primary endpoint of 694 primary CV events. At this time point sites will be notified to bring back all study patients for a final EOS visit. It is at this time patients who have an EOS status obtained will be deemed completed. At this time, any patient who has signed the informed consent, but has not been randomized into the trial will not be eligible to proceed to randomization and should be registered as a screen failure.

Once the study is deemed successfully completed (694 primary CV events reached) or is stopped by the DMC recommendation of overwhelming efficacy (prior to 694 primary CV events reached) or Novartis the following will take place

- All patients with a glycemic status of pre-diabetes will proceed into the 6 month washout phase
- All other patients will continue into an open label extension until such time that study drug is approved for marketing and is available for prescribing physicians and a registry study is approved by local regulatory agencies. At this final open label extension visit, these patients will receive their injections from the sites. The open label extension is then deemed complete and the patient enrolled into the registry study.
- All patients with a glycemic status of pre-diabetes who completed the 6 month wash-out phase will restart study treatment at the end of the washout phase and will continue on to the open label extension phase as noted above.

5.5.11 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, patients should be seen as soon as possible and treated as described in Section 6. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed. Patients should be seen for all visits on the designated day or as close to it as possible. The study assessment schedule below outlines all procedures performed on patients at scheduled visits. The administration of study treatment is performed as per the visit assessment schedule at study sites by trained site staff after the completion of all other assessments.

The visit assessments listed below are for the estimated timeframe a patient would participate in the study. This is an event driven trial and will be stopped when the target number of primary cardiovascular endpoints have been accrued (please see Section 9 for details). All patients will continue study treatments and visits until the event target has been reached. Patients who complete the 36 months will still be required to return to the clinic every 6 months for study assessments and quarterly for study treatment until notified by the site staff of trial completion. Only when the site staff has been notified of the trial completion by Novartis will the patients with a glycemic status of pre-diabetic be asked to enter the 6 month washout phase at their EOS visit.

Patients should attend visits, where labs are drawn, in a fasting state of 10 hours.

Pre-screening is a key element to successfully identifying the correct patients to be screened for this clinical study. All patients should have an available hsCRP value prior to the time of screening. The available hsCRP value should be at least 28 days after a cardiovascular event or procedure or major surgical procedure, and must be less than 60 calendar days prior to screening. The Pre-screening visit should be used after review of the patient's charts to determine patient's eligibility and to obtain an hsCRP value, which is to be run locally, for those potentially eligible patients who do not have one available.

Converting to T2DM: Any patient who is reported as having an elevated HbA_{1c} and/or FPG as defined in Section 4 , will need to have an unscheduled visit within 6 weeks following the first result to assess for conversion from pre-diabetes to T2DM.

Deterioration in Glycemic Control in T2DM Patients: Any patient who is reported as having an elevated $HbA_{1c} \geq 7.5\%$ as defined in Section 6.6.1 , will need to have an unscheduled visit within 6 weeks following the first result to confirm the HbA1c $\geq 7.5\%$.

Discontinuation of study treatment: It is highly encouraged that patients who discontinue study treatment to still attend regularly scheduled clinic visits. If the patient does not attend the scheduled visit, site staff are required to make a telephone contact with the patient to assess for any potential study endpoints and record as appropriately in the eCRFs.

Withdrawal of consent or Lost to Follow-Up: Sites are required to provide an annual update in the eCRF's for any patient who has a status of Withdrawal of consent. Please see Section 5.5.8 For any patient who fails to appear for on site visits the study staff will be required to complete the Visit Information eCRF.

For any patients who suffer from a stroke during the trial please see Section 6.6.4 for details

Sites are required to call the IVRS at the screening visit and at each visit to register their patient's status and if applicable, receive the medication numbers to dispense treatment. Dispensing of medication should be the last assessment performed at each visit.

Table 6-1 Assessment schedule

Visit	Pre-Screen	1	2	2.5	3	4	5	6	7	8	9	10	11	12,16	13,17 [10]	14,18 [10]	15,19 [10]	End of Study (EOS)	End of pre-diabetes washout[5]
Month		-1	**0**	**0.5**	**1.5**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27,39...**	**30,42..**	**33,45..**	**36,48...**	**event driven**	**EOS + 6 months**
Obtain informed consent		X																	
Prescreening Informed Consent	X																		
Height		X																	
Inclusion/Exclusion		X																	
Labs for entry criteria only:, HIV Screen, HBsAg and HCV antibody		X																	
Hs-CRP	X[9]	X	X	X	X	X	X	X	X		X		X		X		X	X	X
Determination of tuberculosis status[1]		X																	
Demography																			
Demography		X																	
History of CV Disease		X																	
Medical History/Current Conditions		X																	
Family History of CV disease			X																
Smoking & Alcohol History			X																
Treatment Assessments																			
Call IVRS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	Pre-Screen	1	2	2.5	3	4	5	6	7	8	9	10	11	12,16	13,17 [10]	14,18 [10]	15,19 [10]	End of Study (EOS)	End of pre-diabetes washout[5]
Month		-1	**0**	**0.5**	**1.5**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27,39..**	**30,42..**	**33,45..**	**36,48...**	**event driven**	**EOS + 6 months**
Drug Dispensing			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X[6]	X
Prior & Concomitant Antidiabetic & CVD Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments																			
Potential endpoint assessment				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c & FPG (all patients)[2]		X	X	X	X	X	X	X	X		X		X		X		X	X	X
Safety Assessments																			
Physical Exam (including weight)			X						X				X				X	X	X
Vitals (includes BMI)		X	X	X	X	X	X	X	X		X		X		X		X	X	X
ECG			X						X				X				X	X	X
Standard Hematology & Chemistry		X	X	X	X	X	X	X	X		X		X		X		X	X	X
Fasting Lipid Profile[3,]		X	X	X	X	X	X	X	X		X		X		X		X	X	X
Other Biomarkers[4]			X			X			X									X	
Immunological (e.g. ANA) Screen			X															X	
Immunogenicity (Anti-			X						X				X					X	

Visit	Pre-Screen	1	2	2.5	3	4	5	6	7	8	9	10	11	12,16	13,17 [10]	14,18 [10]	15,19 [10]	End of Study (EOS)	End of pre-diabetes washout[5]
Month		-1	**0**	**0.5**	**1.5**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27,39..**	**30,42..**	**33,45..**	**36,48...**	**event driven**	**EOS + 6 months**
canakinumab Ab)																			
canakinumab (PK)			X						X				X					X	
IL-1β			X						X				X					X	
Urinalysis including albumin/creatinine ratio (in patients with T2DM or pre-diabetes at baseline)			X			X			X						X			X	X
AE (prompting for infections)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test in women			X															X	

Visit	Pre-Screen	1	2	2.5	3	4	5	6	7	8	9	10	11	12,16	13,17 [10]	14,18 [10]	15,19 [10]	End of Study (EOS)	End of pre-diabetes washout[5]
Month		-1	**0**	**0.5**	**1.5**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27,39...**	**30,42..**	**33,45..**	**36,48...**	**event driven**	**EOS + 6 months**
Other																			
Pharmacogenetics[8]			X																
pharmacogenomic[8]			X			X			X										
EQ-5D			X			X	X		X								X	X	X
SF-36[7]			X		X	X	X	X	X										
MFSI-SF[7]			X		X	X	X	X	X										
Patient Education and Counseling			X																

[1]Please see protocol Section 4.2_ Determination of tuberculosis status for details.

[2] Diagnosis of diabetes or failure of glycemic control based on HbA1c data (and/or FPG for diagnosis of diabetes) should be verified by a repeat HbA1c and FPG within 6 weeks of the initial observation.

[3] Patient must have fasted 10 hours for this test. [3]Triglycerides (TG), total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol and non-HDL cholesterol. LDL Cholesterol, VLDL cholesterol and non-HDL cholesterol will be calculated unless triglycerides > 400 mg/dL in which case only a direct LDL cholesterol assay will be employed.

[4] A panel of biomarkers may include but are not limited to: IL-1Ra, IL-6, IL-18,leptin, adiponectin (total and high MW), TNFα, PAI-1 and fibrinogen

[5] Only patients with pre-diabetes status will enter into this washout period.

[6] Patients who consent to the long-term open-label safety extension will receive their injections at this end of study visit. All those “pre-diabetic” will not receive an injection at the end of study visit, but will enter the 6 month washout period and then enter the long-term open label safety extension thereafter.

[7] Please see Section 6.6.3 and 6.6.4 for administration of the questionnaires in addition to the use of the modified Rankin questionnaire.

[8] Optional for patients and will not exclude them from study participation if declined but

Visit	Pre-Screen	1	2	2.5	3	4	5	6	7	8	9	10	11	12,16	13,17 [10]	14,18 [10]	15,19 [10]	End of Study (EOS)	End of pre-diabetes washout[5]
Month		-1	0	0.5	1.5	3	6	9	12	15	18	21	24	27,39...	30,42..	33,45..	36,48...	event driven	EOS + 6 months

encouraged.

[9] Optional for sites to utilize if there is no documented hsCRP on file for the patient within the protocol specified timeline. This sample should be run locally by the investigator.

[10] This sequence of visits will repeat until the study is deemed complete and sites are notified by the Sponsor to have all patient return for the EOS assessments

6.1 Information to be collected on screening failures

All patients where informed consent has been given (including screening failures), will have the Study Phase Completion eCRF , demographics, inclusion / exclusion, informed consent page and SAE data collected.

For screened patients who signed informed consent but are not randomized or entered into the next epoch of the study (usually starting at visit 1) will have adverse events that are not SAEs followed by the investigator and collected only in the source data.

For all patients who signed the informed consent and are randomized, or who are entered into the next epoch of the study, will have all adverse events occurring after informed consent recorded on the adverse event eCRF page, with the exception of all study endpoints.

The investigator will have the discretion to record abnormal test findings on the medical history eCRF whenever, in their judgment the test abnormality occurred prior to the informed consent signature. For example: an investigator can determine that an ECG abnormality that was seen on an ECG conducted after informed consent was obtained was a pre-existing condition. This pre-existing condition is then recorded on the medical history eCRF and not as an adverse event

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: information on date of birth (if allowable), age, sex, race and ethnicity.

Relevant medical history/current medical conditions present before signing informed consent will be collected at Visit 1. General medical history will include: HEENT, Neoplastic and Hematological Disorders, Cardiovascular history, including MI history, prior events or disease, hypertension, hyperlipidemia, smoking history, Respiratory, Kidneys and Urinary Tract, Gastrointestinal, Immunological and infectious, Endocrine and Metabolic including history and diagnosis of diabetes and it's complications, CNS including psychiatric disorders. Relevant medical history/current medical condition data includes data until signing of informed consent. Where possible, diagnoses and not symptoms will be recorded. Family history for cardiovascular diseases will be collected.

6.3 Treatment exposure and compliance

Study treatment will be administered at the clinic under the supervision of the investigative staff with the dosing record captured within each visit on the Drug Accountability eCRF.

Any medications taken within 30 days prior to the date of screening and after will be recorded on the appropriate Concomitant Medications and or Procedures and Significant Non-drug Therapies eCRF.

6.4 Efficacy

6.4.1 Primary Efficacy assessment (primary objective)

The primary endpoint is defined as the time to the first adjudication committee confirmed major adverse cardiovascular event (MACE) occurring during the double-blind treatment period, which is a composite of CV death, non-fatal MI, and stroke.

An independent adjudication committee that is blinded to treatment assignments will review and adjudicate all clinical events that constitute the primary composite endpoint and secondary endpoints.

6.4.2 Secondary efficacy assessment (secondary objectives)

Key secondary efficacy assessments will comprise:

- Time to the first occurrence of the adjudication committee confirmed composite cardiovascular endpoint consisting of primary endpoint, and hospitalization for unstable angina requiring unplanned revascularization
- Time to adjudication committee confirmed new onset of type 2 diabetes among those with pre-diabetes at randomization (defined in Section 4) (time to NOD)

Other secondary efficacy assessments will comprise

- Time to first event of, non-fatal MI, stroke and all-cause mortality composite
- Time to all-cause mortality

Exploratory efficacy assessments will comprise

- Time to first event of total vascular events composite consisting of primary endpoint, hospitalization for unstable angina, or for any other non-coronary ischemic event (transient ischemic attack or limb ischemia), any revascularization procedure (coronary and non-coronary) and limb amputation
- Other cardiovascular disorders with a known inflammatory component:
    - Time to first deep vein thrombosis/pulmonary embolism
    - Time to first supraventricular tachycardia/atrial fibrillation
    - Time to first stent thrombosis (definite or probable)
    - Time to first hospitalization or prolongation of hospitalization for heart failure
    - Time to first major coronary event (CHD death or MI)
    - Time to first event of coronary revascularization procedures (PCI or CABG)
    - Time to first stroke by etiology
- Explore whether the early high, induction dose regimen in 300 mg canakinumab arm has an impact on early, within 90 days of randomization, primary and secondary clinical cardiovascular event when compared to 150 mg canakinumab arm with no early high, induction dose regimen.

- Glycemic control among those with type 2 diabetes at randomization (defined in Section 4)
  - HbA1c , FPG, and anti-diabetic medication changes by visit from baseline. This analysis includes both longitudinal as well as categorical assessments using HbA1c, FPG, and diabetic medication changes from baseline.
- Failure of glycemic control analyses defined as HbA1c $\geq$ 7.5% (see Section 6.6.1)

Change from baseline in biomarkers of cardiovascular and diabetes risk, including nephropathy by albumin/creatinine ratio in patients with T2DM or pre-diabetes at baseline, inflammatory biomarkers, glycemic control markers, and β-cell function markers

- Change from baseline in patient reported outcomes of tiredness, physical function and performance function and in health status as assessed by the EQ-5D Quality of Life (QOL) assessment.
- Exploratory pharmacogenetic and pharmacogenomic assessments to examine whether individual genetic variation in genes relating to drug metabolism, major cardiovascular event, type 2 diabetes, and the drug target pathway confer differential response to canakinumab.

6.4.3 Appropriateness of efficacy assessments

Time to major adverse cardiovascular events and progression to diabetes (new onset diabetes) are well defined and standard clinical events in clinical trials aimed at demonstrating primary and secondary efficacy of investigational agents on clinical endpoints. Secondary endpoints are widely used clinical efficacy endpoints in cardiovascular clinical endpoint trials. Exploratory endpoints are hypothesis generating and exploratory in nature.

6.5 Safety

Safety and Tolerability Assessments

- Laboratory evaluations
- Weight
- Adverse events and serious adverse events, including cardiovascular events, malignancies, and infections
- Discontinuation due to AEs
- Hypoglycemia events
- Injection site reactions
- Physical Exam
- Biomarkers
- Vitals
- ECG

Serious allergies/immunological events (e.g. Anti-canakinumab antibodies), serious infections, and malignancies adverse events will be monitored carefully using adverse/serious adverse events procedure described in Section 7.1 Adverse events and Section 7.2 Serious adverse event reporting during this trial because these adverse events represent hypothetical

mechanism of action related risks of canakinumab therapy. These adverse events will be adjudicated by an expert adjudication committee to strengthen data quality and safety conclusions.

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing of informed consent must be included in the relevant Medical History/Current Medical Conditions eCRF. Significant findings after the signing of informed consent, which meet the definition of an Adverse Event, must be recorded on the Adverse Event screen of the patient's eCRF.

6.5.2 Vital signs

Vital signs including BP (3 measurements with the average of all three used for inclusion) and pulse measurements will be assessed at as per the assessment. In general blood pressure should be taken after the patient has been sitting for five minutes, with back supported and both feet placed on the floor. Systolic and diastolic blood pressure should be measured three times using an automated validated device with an appropriately sized cuff (for arm circumference of 27 to 34 cm, the cuff should be "adult" size: 16 X 30 cm, for arm circumference of 35 to 44 cm, the cuff should be "large adult" size: 16 X 36 cm, and for arm circumference of 45 to 52 cm, the cuff should be "adult thigh" size: 16 X 42 cm). The repeat sitting measurements should be made at 1 to 2 minute intervals and the mean of the last three measurements will be used. If using the automated devise and current cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Clinically notable vital signs are defined in Appendix 1.

6.5.3 Height and weight

Height in centimeters (cm) or inches and body weight (to the nearest 0.1 kilogram [kg] or pound [lb] in indoor clothing, but without shoes) will be measured. Body Mass Index (BMI) will be calculated as the weight in kg divided by the height in meters squared. Waist circumference should be measured with a flexible tape. For consistency among sites, the position for measuring waist circumference will be at the uppermost border of the right iliac crest (or at the umbilicus if landmarks cannot be palpated). The measure should be recorded while the patient is in the expiratory phase of respiration.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. All patients should be fasting for at least 10 hours prior to having the labs drawn at the scheduled time-points.

Additional samples will be sent to the Central Laboratory for long term storage. Upon completion of the study these samples will be analyzed for cardiovascular and metabolic biomarkers and genetic analysis, if prior written informed consent is obtained

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

The following tests are included in the hematology but are not limited to: HbA1c, Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured.

6.5.4.2 Clinical chemistry

The following tests are included in the chemistry but are not limited to: hsCRP, eGFR, Estradiol, Fasting Plasma glucose, Blood urea nitrogen, creatinine, CK (CK-MB and troponin-I if CK is >2ULN), total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, total protein, albumin, and uric acid will be measured. FSH, HIV screen, HBsAg and HCV antibody will only be measured at V1 for eligibility purposes.

6.5.4.2.1 Fasting Lipid profile

The following tests are included in the fasting lipid profile but are not limited to triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol and non-HDL cholesterol. LDL cholesterol, VLDL cholesterol and non-HDL cholesterol will be calculated unless triglycerides > 400 mg/dL in which case only a direct LDL cholesterol assay will be employed.

6.5.4.3 Urinalysis

Dipstick measurements for specific gravity, protein, glucose and blood will be performed. WBC and RBC sediments will also be measured as a reflex if the dipstick is abnormal. Dipstick will be performed by the central lab. The urine albumin/creatinine ratio will also be measured to assess the presence of micro- or macroalbuminuria in patients with T2DM or pre-diabetes at baseline.

6.5.5 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed at baseline (Visit 2), yearly visits, and at the end of study visit. ECG's will be read by a central vendor. Each ECG tracing should be labeled with the study number, patient initials (if applicable), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities should also be recorded on medical history/ adverse events eCRF page. Any potential endpoints should be recorded on the Clinical Study Endpoint Tracking Form eCRF.

6.5.6 Pregnancy and assessments of fertility

This study does not include women of non-child bearing potential and therefore pregnancy test should be performed to detect unexpected pregnancies. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found

to be negative. If the serum β-hCG is positive, the patient must be discontinued from study treatment but should continue follow up in the trial. Study treatment can be re-started after completion or termination of pregnancy following discussion with the Sponsor.

6.5.7 Appropriateness of safety measurements

Safety endpoints used in this trial are standard endpoints in demonstrating safety of investigational agents in clinical trials. Safety events of special interest in the following categories will be adjudicated by expert adjudication committee. Allergies/ Immunological events, serious infections and malignancies. Additionally, canakinumab and canakinumab antibody concentrations will be measured due to the hypothetical risk of immune response to the study treatment. These safety events of special interest represent hypothetical risks of canakinumab treatment.

6.6 Other assessments

6.6.1 Assessment of durability of glycemic control for T2DM (exploratory endpoint)

These analyses are performed for patients with type 2 diabetes mellitus (T2DM) at randomization (defined in Section 4).

Patients with T2DM at randomization may be treated with any anti-diabetic medicine approved for use by local health authorities.

Long term glucose control durability of canakinumab will be assessed in patients with T2DM and HbA1c<7.0% at randomization by performing failure of glycemic control analysis. The first assessment of failure of glycemic control is at 6 month visit and thereafter every 6 months. Failure of glycemic control is defined as HbA1c $\geq$ 7.5% confirmed by a second HbA1c measurement within 6 weeks of the initial result. During this trial investigators should increase anti-diabetic medications or start new anti-diabetic medications only after HbA1c $\geq$ 7.5% has been confirmed.

6.6.2 Healthcare Resource Utilization

Healthcare Resource utilization data will not be collected in this study

6.6.3 Patient Reported Outcomes

Patient reported outcomes (PRO) have been identified as important in the post MI patient population. While a variety of relevant concepts within the context of canakinumab have been identified, the concepts of tiredness, physical function and performance function have been selected as prioritized measurement concepts. In order to measure these concepts a set of PRO instruments will be administered.

The PRO instruments to be included in this trial, where available, are the SF-36, the Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF) and the EQ-5D. Details on each of these instruments are provided in addition to the target population.

For onsite visits only, it is strongly encouraged patients complete the questionnaire(s) before other clinical assessments.

Completed questionnaires will be reviewed and examined by the investigator before the clinical examination for responses, which may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also any unsolicited comments written by the patient

If the occurrence of AEs or SAEs is confirmed, the physician must record the events as per instructions given in Section 7.1 of the protocol. Investigators should not encourage the patients to change the responses reported in the PRO questionnaires

Patient Reported Outcome Measures

Baseline Post MI

1. **SF-36**

   Target population: Patients who are post MI 30 days to less than 6 months in US and pre-defined EU countries.

   The SF-36 has been selected to measure physical and performance function amongst patients post MI at several time points throughout the trial. The SF-36 is a 36 item measure developed by Cathy D. Sherbourne and John E. Ware. The SF-36 encompasses generic health concepts considered to be relevant across age groups, disease states and treatments types and has been validated in many disease states. For the purposes of this trial we will focus on the physical function and physical role domains, however the full instrument will be completed. The SF-36 will take patients approximately 5-10 minutes to complete. For this trial, the acute version of this measure, which includes a one week recall period, will be utilized.

   The SF-36 will be administered, where available, to patients enrolled in trial sites located in the U.S. and countries under the authority of the E.M.A. only. In addition, only patients who had a MI 30 days to less than 6 months of their enrollment date will be targeted for completing the SF-36. The SF-36 will be given to patients to complete in clinic as per the study assessment schedule.

2. **MFSI-SF**

   Target population: Patients who are post MI 30 days to less than 6 months in US and pre-defined EU countries.

   The MFSI-SF is a 30 item measure developed by Danette Hann, Paul B. Jacobsen, and Kevin D. Stein. The MFSI-SF encompasses a wide spectrum of concepts related to fatigue including physical, mental and emotional tiredness. This instrument has a 7 day recall period and is expected to take approximately 5 minutes for patients to complete. This instrument has been selected to measure tiredness in patients post MI and post stroke at several time points throughout the trial.

   The MFSI-SF will be administered, where available, to post MI patients enrolled in trial sites located in the U.S. and countries regulated under the authority of the E.M.A. only. In addition, only patients who had a MI 30 days to less than 6 months of their enrollment date will be targeted. The MFSI-SF will be given to patients to complete in clinic as per the study assessment schedule

3. **EQ-5D**

Target population: All patients enrolled in the trial

Generic multidimensional health-related quality of life will be assessed with the EuroQoL (EQ-5D). The EuroQol EQ-5D is a simple but effective standardized instrument designed for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides both a compact descriptive profile and a single index value that can be used in the clinical and economic evaluation of health care.

The EQ-5D measures five domains (mobility, self-care, usual activity, pain/discomfort & anxiety/depression).

There are two parts to this questionnaire. The first, 'health state classification' consists of five questions. The second, 'Visual Analogue Scale Thermometer' consists of a visual analogue scale. This generates a self-rating of current health-related quality of life. This will be used with the health state classification to build a composite picture of the respondent's health status.

- Data capture

EQ-5D enables an accurate self-description of current health-related quality of life to be easily recorded. Self-explanatory instructions to respondents are provided within the questionnaire and it takes about two minutes to complete.

- Health State Classification

The first page consists of five questions. The respondent is asked to indicate his/her current health state, by ticking the most appropriate of three statements about each of the five quality of life dimensions.

Each statement represents an increasing level of severity (1=no problem, 2=some or moderate problem, 3= unable or extreme problem). For example, a respondent with 'no problem' for each of the five questions will be said to have a health status of 11111.

- Visual Analogue Scale 'Thermometer'

The 'Thermometer' has end points of 100 (best imaginable health state) at the top and 0 (worst imaginable health status) at the bottom.

The respondent will rate his/her current health status by drawing a line from the box marked 'Your health status today' to the appropriate point on the 'thermometer' scale.

The site staff should record the two digit reading on the thermometer (where the line by the respondent crosses the thermometer) on the appropriate space in the CRF.

Missing or ambiguous values will be left blank.

Note: Questionnaire should be completed by the patient at the center, where available, before any other assessments take place.

6.6.4 Stroke Functional Assessment Sub-Study

Pre-clinical models indicate that anti-inflammatory therapy and specifically IL-1β blocking therapy may limit the size of stroke impact in brain tissue and facilitate functional recovery

from stroke. Therefore, this clinical trial includes a sub-study on functional assessment of the patients recovering from stroke experienced during this trial and agreeing to participate in this sub-study in order to support the hypothesis that canakinumab therapy facilitates functional recovery from stroke.

The following 3 assessments will be performed on all patients who have suffered a stroke during the trial.

6.6.4.1 The Modified Rankin Scale

Performed 30 and 90 days post stroke: The effects of canakinumab on patients who undergo an ischemic stroke during the study and washout period will be assessed using the Modified Rankin scale (mRS), which provides an assessment of overall global neurologic function through serial observation of a patient's ability to perform Activities of Daily Living (ADL). A diagnosis of ischemic stroke will be determined by usual Standard of Care, and will include neurologic signs and symptoms of ischemia accompanied by radiologic studies, which confirm the clinical diagnosis, as well as eliminating hemorrhagic stroke as a possible cause.

Patients will be examined at 30 and 90 days post-stroke by a Consulting Neurologist, who will score the serial examinations as noted below. Day 90 post-stroke assessment will be the primary outcome of this sub-study.

Grade Description

0 No symptoms at all

1 No significant disability despite symptoms: able to carry out all usual duties and activities

2 Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance

3 Moderate disability: requiring some help, but able to walk without assistance

4 Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance

5 Severe disability: bedridden, incontinent, and requiring constant nursing care and attention

6 Death

6.6.4.2 MFSI-SF

Performed 30 and 90 days post stroke: Any patient who has a stroke at any time after enrollment in the trial will be targeted to complete the MFSI-SF instrument, where available, 30 days and at month 3 post their stroke event to assess tiredness. Any patient in the US or predetermined EU countries, who is to completing the MFSI-SF as a post MI patient and then has a stroke event (also recurrent stroke events) will also complete this questionnaire.

6.6.4.3 SIS-16

Performed 30 and 90 days post stroke: The SIS-16 has been selected to measure physical function and performance function in patients post stroke at several time points throughout the trial. The SIS-16 is a 16 item measure, which was developed by Pamela W. Duncan. The SIS-

16 encompasses a spectrum of concepts for physical function and performance function specific to stroke. The instrument utilizes a 2 week recall period.

The SIS-16 will be administered, where available, at all trial sites to any patient who has a stroke occur at any time after enrollment as well recurrent stroke events. The SIS-16 will be given to patients to complete in clinic at 30 and 90 days post their stroke event.

6.6.5 Pharmacokinetics

6.6.5.1 Blood collection

All blood samples must be taken at each indicated visit prior patient receiving their study medication injections. Blood samples will be taken at any time point by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

For each scheduled PK sample, 2 mL of blood will be drawn into a plain barrier tube, to obtain 1.5 mL serum. The sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. The sample will be split into **two** aliquots to be transferred into freezer-proof polypropylene screw-cap tubes. Serum tubes will be frozen within 90 min of venipuncture and kept at ≤ -18°C pending shipment on dry ice. One of the two serum samples is to be kept at the study site as a backup while the other one will be shipped to the central lab.

For a detailed description of blood sampling schema, please refer to the Blood Log in Appendix 2

Time points for collection:

- Baseline (Month 0): pre-dose
- Month 12 (pre-dose)
- Month 24 (pre-dose)
- EOS (pre-dose for all normoglycemic and Type 2 diabetes mellitus patients)

6.6.5.2 Analytical method(s)

An ELISA method will be used for bioanalytical analysis of canakinumab in serum, with an anticipated lower limit of quantification (LLOQ) of 100 ng/ml. The detailed method description to assess canakinumab concentration will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR)

6.6.5.3 PK sample handling, labeling and shipment instructions

6.6.5.3.1 Sample labeling

The samples for the pharmacokinetic profile will be labeled as follows:

PK

Study Code: CACZ885M2301

Patient Number:

Sample Number:

Date / Study Day:

Required Time:

Labels will be provided to the investigator.

For each shipment, the same procedure described in Section 6.6.5.3 PK sample handling, labeling and shipment instructions has to be followed.

6.6.6 Pharmacodynamics

Total IL-1β (sum of free and bound canakinumab) will be determined in serum.

Pharmacodynamic (PD) samples are to be collected at visits shown in Table 6-1.

6.6.6.1 Blood collection

All samples must be taken prior receiving their injections All blood samples will be taken, prior to dosing, by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

For each scheduled PD sample, 3 mL of blood will be drawn into a plain barrier tube, to obtain 1.5 mL serum. The sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. The sample will be split into two aliquots to be transferred into freezer-proof polypropylene screw-cap tubes. Serum tubes will be frozen within 90 min of venipuncture and kept at ≤ -18°C pending shipment on dry ice. One of the two serum samples is to be kept at the study site as a backup while the other one will be shipped to the central lab.

For a detailed description of blood sampling schema, please refer to the Blood Log in Appendix 2

Time points for collection:

- Baseline (Month 0): (pre-dose)
- Month 12(pre-dose)
- Month 24 (pre-dose)
- End of study

PD parameters: Total IL-1β in serum, this being the sum of free and bound canakinumab; rate of IL-1 production, clearance, and its binding affinity to canakinumab.

6.6.6.2 Analytical method(s)

Total IL-1β will be analyzed in serum by means of a competitive ELISA assay, limit of detection (LOD) at 0.25 pg/ml.

Details of the analytical methods to assess total IL-1β in serum will be described in the bioanalytical data report.

6.6.6.3 PD sample handling, labeling and shipment instructions

6.6.6.3.1 Sample labeling

The samples for the pharmacodynamic profile will be labeled as follows:

PD

Study Code: CACZ885M2301

Patient Number:

Sample Number:

Date / Study Day:

Required Time:

Labels will be provided to the investigator.

For each shipment, the same procedure described in Section 6.6.6 PK sample handling, labeling and shipment instructions has to be followed.

6.6.7 Immunogenicity assessments

Anti- canakinumab antibodies concentrations will be assessed in serum.

Blood samples for Immunogenicity (IG) assessments are to be collected at visits shown in Table 6-1.

6.6.7.1 Blood collection

For each scheduled IG sample, 1 mL of blood will be drawn into a plain barrier tube, to obtain 500 µL serum. The blood sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. Serum tubes will be frozen within 90 minutes of venipuncture and kept at ≤ -18°C pending shipment on dry ice.

If anaphylactoid reactions occur after injection, two more samples (at the time of the event and 8 weeks later) need to be taken.

6.6.7.2 Immunogenicity sample handling, labeling and shipment instructions

6.6.7.2.1 Sample labeling

The samples for the IG profile will be labeled as follows:

Anti- canakinumab Detection

Study Code: CACZ885M2301

Patient Number:

Sample Number:

Date / Study Day:

Required Time:

Labels will be provided to the investigator.

For each shipment, the same procedure described in Section 6.6.5.3 PK sample handling, labeling and shipment instructions has to be followed including sending a back up sample.

6.6.7.3 Analytical method(s)

IG is analyzed by BIAcore. The system monitors the interaction between two molecules, of which one is attached to the sensor surface and the other if free in solution. In this assay, canakinumab is reversibly bound to protein G, which is covalently bound to the specific sensor surface on which the serum samples are injected. Binding of potential anti-canakinumab antibodies is detected in real time as mass accumulation on the sensor surface. The detection is based on Surface Plasmon Resonance.

Details of the analytical methods to assess anti- canakinumab antibodies in serum will be described in the bioanalytical data report.

6.6.8 Pharmacogenetics/pharmacogenomics

The study includes an optional pharmacogenetic and pharmacogenomic component which requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents these options to the patient. Should a patient choose not to participate in the pharmacogenetics or pharmacogenomic sampling they may still continue into the trial.

Lab manuals will be provided with detailed information on sample collection, handling, and shipment. The sample collection date must be entered on the CRF (eCRF) page.

Any genetics sample that remains after analysis may be stored for up to 15 years to address scientific questions related to canakinumab, major cardiovascular event or type 2 diabetes.

Pharmacogenetics

Exploratory pharmacogenetics research studies are planned as a part of this study with the objectives of identifying inherited genetic factors, which may (1) be related to major cardiovascular event, type 2 diabetes, hemostasis, inflammation, lipid, and/or coagulation disorders (2) predict response to treatment with canakinumab, or (3) predict genetic predisposition to side effects. We hope to develop a better understanding of major cardiovascular event and type 2 diabetes, and how patients respond to canakinumab.

Sample collection: One 10 mL blood sample will be collected at baseline (Visit 2) in an EDTA tube. After collection, the sample must be inverted several times to prevent clotting. If the blood draw at Visit 2 is missed, the sample should be taken at the next visit that a blood draw is already scheduled. Only one blood sample should be taken from the patient for this pharmacogenetic study. These samples will be shipped to the central lab.

Pharmacogenomics

Pharmacogenomics studies will be done to identify gene expression (mRNA) patterns of blood cells that are associated with treatment response to canakinumab, or that possibly correlate with the severity or progression of disease.

Sample collection: Two 2.5 mL blood samples will be collected in PAXgene tubes at baseline, month 3 and month 12 visits. These samples will be shipped to the central lab.

6.6.9 Other biomarkers

Biomarker measurements will be obtained on all patients at the visits indicated in the study assessment schedule. A panel of biomarkers may include but are not limited to:. IL-1Ra, IL-6, IL-18, leptin, adiponectin (total and high MW), TNFα, PAI-1 and fibrinogen .

Additional samples will be sent to the Central Laboratory for long term storage. Upon completion of the study these samples will be analyzed for cardiovascular and metabolic biomarkers and genetic analysis, if prior written informed consent is obtained

7 Safety monitoring

7.1 Adverse events

An adverse event is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing informed consent.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria they induce clinical signs or symptoms, they are considered clinically significant or they require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study

Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values, which are considered to be non-typical in patient with underlying disease

All adverse events, which are non protocol endpoints, must be recorded on the Adverse Events CRF with the following information:

1. the severity grade [mild, moderate, severe]
2. The relationship to the study treatment (Reasonable possibility that the AE is related: No, Yes)
3. Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported at the time of the end of the study
4. whether it constitutes a serious adverse event (SAE)
5. the action taken regarding study treatment
6. whether medication or therapies taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

7. the outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

An SAE is defined as any adverse events (appearance of or worsening of any pre-existing condition, undesirable sign(s), symptom(s) or medical condition, which are not protocol endpoints, that meet the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Study-specific adaption of the standard definition of AEs and SAEs

In order to avoid double reporting and unblinding of study endpoints, a study specific exemption has been granted from the Health Authorities not to report study endpoints as serious adverse events/adverse events. Therefore, any cardiovascular event sent for adjudication as a potential study endpoint or is reported as non-adjudicated cardiovascular endpoint by the investigator will not be reported as an adverse event /serious adverse event but will be captured on the Clinical Endpoint Form eCRF. Only if adjudication committee determines that the event is not a study endpoint, will this event be reported as an adverse / serious adverse event following procedures described in Section 7.2 Serious adverse event reporting.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2**.**

All adverse events should be treated appropriately. Action taken may include one or more of the following: no action taken (i.e. further observation only); study drug dosage temporarily interrupted; study drug permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent. - Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, suspected relationship to the study treatment, interventions required to treat it, and outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new Adverse Experiences (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonable be related to study treatment. This information should be recorded in the investigator's source documents, and if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, except for those being adjudicated as endpoints or are reported as non-adjudicated cardiovascular endpoint by the investigator, which occur after the patient has provided informed consent and until 90 days after the last study visit (following the last administration of study treatment if there are post-treatment follow-up visits) must be reported to Novartis within 24 hours of learning of the occurrence. Any SAEs experienced after this 90 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Hypoglycemia events, which require hospitalization or the assistance of another person to treat must, be reported as an SAE.

Information about all SAEs (either initial or follow-up information) may be collected and recorded on the electronic Serious Adverse Event Report Form that is part of the study eCRFs. If, for any reason, the SAE information (or follow-up information)can not be entered into the electronic SAE form within 24 hours of becoming aware of the SAE (or the follow-up information), the information must be recorded on the paper SAE Form and faxed to Novartis. The investigator must assess the relationship of any SAE to study drug(s), complete the eCRF or paper SAE Report Form in English.

When SAEs are recorded in the electronic SAE form, these data will automatically be submitted to Novartis after investigator signature or after 24 hours of entry, whichever occurs first

When the SAEs are recorded on paper SAE forms, these should be fax within 24 hours of awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department . The telephone and telecopy number of the contact persons in the local department of Clinical Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or

progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Reporting of events (including coincidental cardiovascular events) that are both study endpoints and AE's / SAE

The integrity of this study may be compromised if cardiovascular events that are study endpoints are systematically unblinded in order to fulfill European SUSAR reporting requirements for SAE (European Commission ENTR/CT3 Guideline (2006)). Therefore, in this study, potential study endpoints are excluded from the definition of AE's and SAE's and are not to be captured as AE and SAE's but only on the relevant study endpoint CRF. These events are therefore NOT to be reported to Novartis within 24 hours on SAE forms and will not be reported to regulatory agencies or investigators other than as a study endpoint in the Clinical Study Report. Reporting to IRB's should follow local guidelines. .

The following pre-defined study endpoints are excluded from the definition of AEs and SAE's in this trial:

- CV and non-CV Deaths (please see section Reporting of Deaths for specific exceptions for selected non-CV deaths that must be reported as both endpoints AND SAEs)
- Fatal and non-fatal MI
- Fatal and non-fatal Stroke (e.g. hemorrhagic stroke, ischemic stroke)
- Unstable angina requiring unplanned coronary revascularization
- Stent Thrombosis (per ARC definition)
- Hospitalization or prolongation of hospitalization for heart failure
- Critical Limb ischemia
- Limb amputation
- Transient Ischemia Attack (TIA)
- New onset type 2 diabetes (NOD)
- Non-Coronary revascularization procedures
- Coronary angiography / Coronary Revascularization (PCI or CABG)
- Atrial fibrillation/ atrial flutter/ supraventricular tachycardia
- Pulmonary embolism and deep vein thrombosis

The Data Monitoring Committee (DMC) will review these endpoint data throughout the trial in an unblinded manner. Should the DMC make recommendations on the conduct of the trial that are considered to have significant bearing on the benefit risk of the trial, these will be communicated to competent authorities, IRBs/IECs and investigators and the ECs by Novartis in an appropriate timescale.

Any event that is not listed under the pre-specified endpoints above should be reported as an SAE. If it meets SUSAR criteria, it will be unblinded; a report to competent authorities and relevant ethics committees and issuance of an IND Investigator Safety Letter will occur per local regulatory requirements.

Should an investigator consider that the character and the severity of the above listed events is not consistent with the expected presentation or course of that endpoint and the investigator considers that the study drug may have contributed to this abnormal presentation, then this event should be reported as an SAE and an endpoint.

Should an investigator report an SAE that is considered by Novartis to be potentially consistent with a study endpoint, Novartis will request confirmation from the investigator that this event is indeed an SAE and not an endpoint. The investigator should respond immediately to these requests in order to minimize the risk that such an event may require unblinding for regulatory reporting of SUSARs. Should the investigator, following this request for review, consider the event to be an endpoint the event must be included as an endpoint and confirmation sent to Novartis DS&E that the event should no longer be considered an SAE. Should the investigator either fail to reply in the necessary timeframe, or confirm that the event is an SAE and not an endpoint, the event will be handled as an SAE.

Events that following data review and adjudication are deemed not to be endpoints for this study will be reported as AEs and SAEs, as soon as adjudication process has been completed, following standard reporting guidelines.

Reporting of deaths

It is important to note that ALL deaths (deaths considered by the investigator to be CV and non-CV causes) must be reported as predefined study endpoints and the investigator must send all documentation for adjudication.

The following SAEs have been causally associated with non-CV deaths due to various medications in the past. Therefore, if a patient during this study, is considered to have died as a result of any of the following events, the death must be reported as both an endpoint AND as SAE. The SAE must be reported to Novartis as per SAE reporting guidelines.

NON-CV FATAL EVENTS THAT ARE REPORTED AS BOTH DEATH ENDPOINTS AND SAEs

- Allergy events: Anaphylaxis, Angioedema, Laryngeal edema
- Serious hepatic events including hepatic failure, hepatic necrosis, Hy's law case, acute yellow liver atrophy

- Serious cutaneous skin reactions including: Stevens-Johnson syndrome, Toxic epidermal necrolysis, Erythema multiforme
- Drug induced hematological syndromes (including agranulocytosis, aplastic anemia, bone marrow failure, pancytopenia and bicytopenia)
- Inflammatory lung disorders (including allergic, fibrosing, and necrotising alveolitis, eosinophilic pneumonia and interstitial lung disease)
- Autoimmune myocarditis
- Suicide including drug overdose
- Malignant hypertension
- Pulmonary hypertension
- Renal failure (acute and chronic) including tubulointerstitial nephritis
- Hyperpyrexia, Hyperthermia malignant
- Opportunistic infections
- Systemic lupus erythematosus
- Hypoglycemia
- Torsade de pointes, Long QT syndrome
- Pancreatitis
- Drug interaction
- Rhabdomyolysis
- Seizure
- Guillain-Barre syndrome
- Progressive multifocal leukoencephalopathy (PML)

7.3 Pregnancies

Women of child-bearing potential are excluded from this study; however, in the event a woman became pregnant we must ensure patient safety. Each pregnancy in a patient on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.4 Data Monitoring Committee

An external and independent DMC will be formed for this trial to periodically review safety information, and to evaluate the interim results relative to pre-defined statistical criteria to see if the trial has reached standards allowing stopping for proof of efficacy or for futility

The DMC will include experts in cardiovascular and cerebrovascular disease, T2DM, large scale clinical trials and statistics; the members will review the results confidentially and will have no other roles in the study.

The membership of the DMC and the responsibilities of the DMC and Novartis will be defined in a separate document entitled the "Data Monitoring Committee Charter." The DMC Charter will include information about the data flow, purpose, timing of DMC meetings, guidance in the decision-making process, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest, and statistical monitoring guidelines.

7.5 Adjudication Committees

There will be two separate adjudication committees for this study.

7.5.1 Cardiovascular clinical events adjudication committee

Cardiovascular clinical events will be adjudicated under blind by an adjudication committee, composed of reviewers who are experts on cardiovascular and cerebrovascular disease and T2DM. This measure is designed to ensure the objectivity, reliability and validity of the event classification. The procedures for reporting and case definitions are detailed in a separate charter document. The following primary and secondary cardiovascular endpoints will be adjudicated:

- All death
- Non fatal MI
- Stroke (e.g. hemorrhagic stroke, ischemic stroke)
- Unstable angina requiring unplanned coronary revascularization
- New onset type 2 diabetes mellitus

Definitions of clinical endpoints are described in Appendix 3.

The primary endpoint will be assessed based on MACE adjudicated to have occurred between a patient's randomization and either

1. the patient's entry into the wash-out period,
2. or the patient's entry into the long-term safety extension study,
3. or for those patients not proceeding to neither wash-out period or safety extension the patient's end of study visit, but only if it occurred during the close-out period,
4. or otherwise the end of the close-out period (analysis cut-off).

Thus, events occurring after informed consent but before randomization do not need to be adjudicated and should instead be reported as adverse or serious adverse events. Events occurring in the safety extension study should be reported as specified in the clinical trial protocol for the safety extension study.

Baseline and yearly ECG will be obtained to assess interval ECG changes for study patients. Myocardial infarctions detected as interval ECG changes without clinical sequelae ("silent myocardial infarction") will be reported as endpoint. Interpretation of all scheduled ECGs will be done by a central ECG vendor (eRT, Philadelphia, PA) using qualified expert physicians.

The diagnosis New MI should be used when an ECG shows an MI that was not present on previous ECGs for the study patient. Previous ECGs must be available. This diagnosis should be used the first time the new MI is seen, but not for subsequent ECGs.

7.5.2 Allergy, serious infections and malignancies Adjudication Committee (AIM)

New allergy, serious infections and malignancies (whether newly detected or worsening of an existing non-basal cell malignancy) will be adjudicated by a separate expert committee composed of experts in allergy/immunology, infectious diseases, and oncology. This measure is designed to ensure the objectivity, reliability and validity of the event classification. The procedures for reporting and case definitions are detailed in a separate charter document.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis or study team representative will review the protocol and (e)CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on (e)CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the (e)CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the (e)CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data (either paper or CD-ROM) for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug dispensed to the patient will be tracked using an Interactive Voice Response System (IVRS/IWRS). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete for the main study (i.e. excluding the washout period and long-term open-label safety follow-up extension study, which will be reported separately) and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Clinical Science Unit Head and the IIS Program Head.

Each occurrence of a code break via IVRS/IWRS will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Pharmacogenetic/Pharmacogenomic samples:

To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the patient's information and identity. This double-coding process allows the destruction of the sample at the patient's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

The use of pharmacogenetics to search for biomarkers of disease and drug action is exploratory. Any results from this pharmacogenetic study will not be placed in the patient's medical records.

9 Data analysis

9.1 Analysis sets

The following analysis populations will be defined for statistical analysis:

- **Screened set** – All patients who signed the informed consent.
- **Randomized set** – All patients who received a randomization number, regardless of receiving trial medication.
- **Safety set (SAF)** – All patients who received at least one dose of study treatment and have at least one post-baseline safety assessment. Of note, the statement that a patient had no adverse events also constitutes a safety assessment. Patients will be analyzed according to treatment received. Treatment received will be considered identical to the randomized treatment if the patient has during at least one visit received at least one (of the two) injections constituting the treatment assignment at randomization and no wrongly administered injections constituting a different treatment group.
- **Full analysis set (FAS)** – All randomized patients. This is the primary efficacy population applied in all efficacy endpoints. Following the intent-to-treat principle, patients are analyzed according to the treatment they have been assigned to at the randomization. However, patients who have not been qualified for randomization and who have been inadvertently randomized into the study are excluded from FAS, provided these patients have not received study treatment.
- **Per protocol set (PPS)** – a subset of the FAS, consists of all randomized patients in FAS who take at least one dose of study medication and have no major protocol deviations affecting the primary endpoint analyses. Major protocol deviations leading to exclusion from PPS will be specified prior to database lock on a blinded basis and documented in a separate document.

Note: The last part of the definition of the FAS is what is often referred to as misrandomized patients; i.e. patients for whom IVRS calls were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomization eligibility and double-blind medication was not administered to the patient. These patients would subsequently not continue to take part in the study or be followed-up. Misrandomized patients will not be included in the FAS, but they will be included in the Randomized Set. Further exclusions from the FAS may only be justified in exceptional circumstances.

9.2 Patient demographics and other baseline characteristics

The number of patients screened, randomized and included in FAS will be presented by treatment group and overall for the screened set. In addition, the reasons of screen failures will be provided for screened set as well. The number and percentage of patients in the randomized set who completed the study, who discontinued the study and the reason for discontinuation will be presented for each treatment group and all patients. The frequency (%) of patients with major protocol deviations as well as the criteria leading to analysis sets will be presented in separate tables for the randomized set. Finally, the number of enrolled and randomized patients by region as well as the number of patients enrolled and randomized per region and country will be presented descriptively for the randomized set.

Baseline value is defined as the last non-missing assessment prior to the first dose of randomized study medication unless specified otherwise.

The following common background and demographic variables will be summarized using descriptive summary statistics (for continuous variables mean, median, standard deviation, Q1 (25^{th} percentile), Q3 (75^{th} percentile), minimum and maximum and for categorical variables frequency and percentage):

- Age [years]
- Sex
- Race
- Ethnicity
- Height [cm]
- Weight [kg]
- Body mass index [kg/m^2] calculated as weight [kg]/ $height^2$ [m^2]
- Waist circumference [cm]
- Sitting pulse [bpm]
- Mean sitting SBP [mmHg]
- Mean sitting DBP [mmHg]
- Smoking history
- Alcohol history
- Region (Country) of enrollment
- Cardiovascular risk factors and other co-morbidities including but not limited to following:
    - Diabetes mellitus, complications of diabetes
    - Hypertension
    - Dyslipidemia/Hyperlipidemia
    - Atrial fibrillation
    - Supraventricular tachycardia
    - Deep Vein Thrombosis
    - Pulmonary embolism

- Prior repeated MI (multiple MIs in medical history)
- Prior PCI
- Prior stent implantation (incl. drug eluding stent or bare metal stent)
- Prior CABG
- Prior TIA/stroke
- Congestive heart failure

- Medical history of gout
- Post MI index group
- hsCRP [mg/L (two values available with the mean of these two used in analysis)]
- HbA1c [%]
- FPG [mmol/L]
- Lipid profile
- Glycemic status: T2DM, pre-diabetes, normoglycemic
- Level of exercise
- Family history of MI, stroke or diabetes
- Highest degree of education

Treatment group comparability will be examined using the Cochran-Mantel-Haenszel test for the categorical variables and the F-test for the continuous variables as appropriate. These p-values will be provided for descriptive purposes and will not be considered to define any formal basis for determining factors that should be included in statistical models. If imbalances between treatment groups with respect to some variables occur, additional supplemental analyses may be performed to assess the impact of these imbalances as appropriate.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Study drug

The duration of the double-blind treatment will be computed as the time from the first injection to the first out of

1. the last injection date plus a quarter year (91 days),
2. the patient's death
3. or the patient's study completion visit during the study close-out period.

This algorithm reflects the planned treatment schedule and the long half-life of the study drug. The duration of the treatment period will be summarized for the full analysis set and safety set by treatment group descriptively including by duration categories. The overall patient-years of treatment will be computed as the sum of patient years of double-blind treatment for all patients.

Duration of exposure to study treatment excluding interruptions will be computed and summarized as above, but not counting periods during which the last injection was more than a quarter year ago.

Prior and concomitant therapies

Prior or concomitant medications will be summarized for the safety set in separate tabulations based on the coding dictionary used. Medications will be presented in alphabetical order, by preferred terms and grouped by anatomical main group. Tables will show the overall number and percent of patients receiving at least one drug of a particular preferred term and at least one drug in a particular anatomical main group.

Prior medications and significant non-drug therapies are defined as any medications and significant non-drug therapies taken prior to the randomization visit. Concomitant medications and significant non-drug therapies are defined as those used during the double-blind period. Concomitant medications that were prohibited as per protocol and given during the conduct of the study as well as significant non-drug therapies will be summarized.

Furthermore, the following classes of medications to be precisely defined in the statistical analysis plan, at time of randomization and during the double-blind period, which are relevant to program indication, will be summarized separately:

- Anti-ischemic agents
  - Beta blockers
  - Intravenous or oral nitrates
  - Calcium channel blockers
- Anti-platelet agents
  - Acetylsalicylic acid (aspirin)
  - Non-aspirin oral anti-platelet agents (like P2Y12 inhibitors clopidogrel and prasugrel)
- ACE inhibitors (like ramipril)
- ARBs
- Lipid-lowering agents
  - Statins
  - Non-statins (like fibrates, binding resins and nicotinic acid)
- Diuretics
  - Thiazide diuretics
- Anti-diabetic medications
  - Insulin
  - Thiazolidinediones
  - Other oral hypoglycemic agents
- Proton pump inhibitors
- Anticoagulants

9.4 Analysis of the primary variable(s)

The primary analysis and all analyses of secondary/exploratory endpoints will use the Full Analysis Set (FAS), which reflects the intention-to-treat principle.

Unless otherwise specified all time-to-event analyses will be based on events occurring during the double-blind treatment period. This means that only events between a patient's randomization and either

1. the patient's entry into the wash-out period,
2. or the patient's entry into the long-term safety extension study,
3. or for those patients not proceeding to neither wash-out period or safety extension the patient's end of study visit, but only if it occurred during the close-out period,
4. or otherwise the end of the close-out period (analysis cut-off) will be counted in these analyses.

9.4.1 Variable

The primary efficacy variable is the time to first occurrence of a major adverse cardiovascular event (MACE), which is a composite endpoint consisting of cardiovascular death, non-fatal MI, and stroke. An independent adjudication committee will review and adjudicate all clinical events that constitute the composite of the primary endpoints on a blinded basis.

The time-to-event is computed as the number of days from randomization to the onset of the primary endpoint event. Data on patients who do not reach the primary endpoint by the study end date will be censored at the latest date they are known to be at risk.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary statistical null hypotheses are

- H_{11}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 150 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{21}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 300 mg dose group is greater than or equal to the hazard rate of the placebo group.

Each null hypothesis is tested against the one-sided alternative that the hazard rate is smaller for the respective active dose group than for the placebo group.

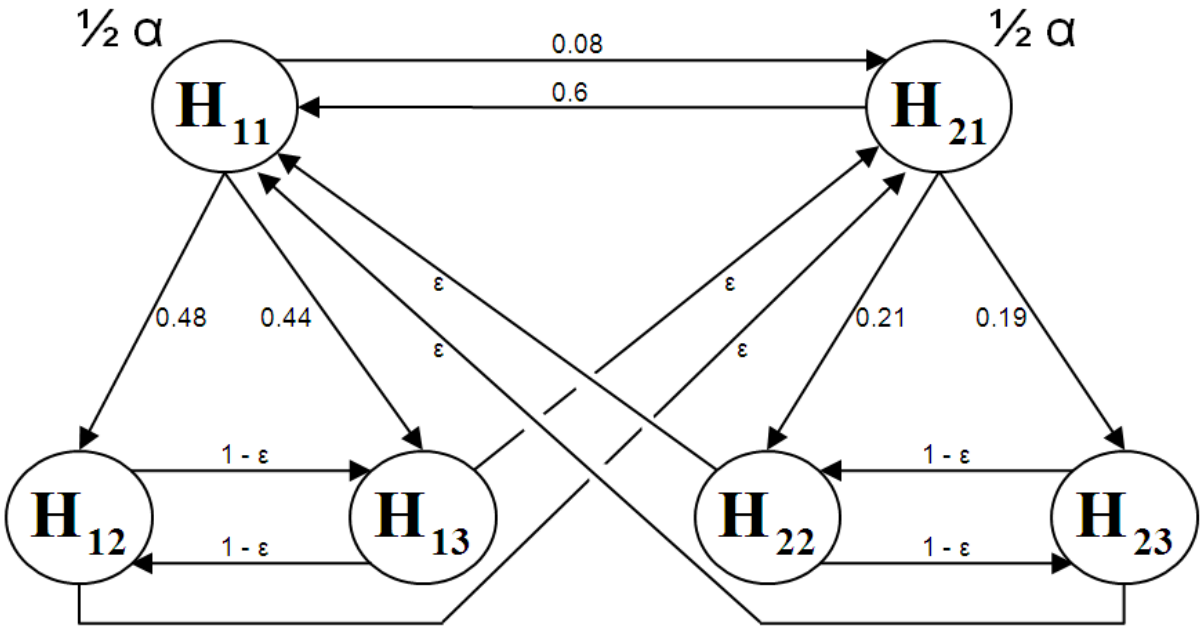
These hypotheses will be tested by comparing each dose to placebo with a log-rank test stratified by time since index MI (30 days to < 6 months and ≥ 6 months) using Peto's exact method (Peto 1972) for handling ties on the full analysis set (FAS) according to the intent-to-treat principle. The family-wise error rate will be controlled at the two interim analyses and the final analysis using the closed testing procedure shown in Figure 9-1 using the graphical method of (Bretz, et al 2009); however, intersection null hypotheses involving the primary null hypotheses for both doses will be tested using Dunnett's test (Dunnett 1955). Specifically this means that for any intersection hypothesis from the full closure that contains both H_{11} and H_{21}, a Dunnett test for H_{11} and H_{21} is performed at the full significance level for the respective analysis (at the final analysis 2.45%), while all other hypotheses in that intersection receive zero weight. All other intersection hypotheses are tested with a weighted Bonferroni test. Protection of the family–wise error rate at level alpha is still guaranteed when the transition

weights on the directed edges are chosen as in Figure 9-1 (see comment below) and all the tests on secondary variables are performed at the level resulting from the graphical procedure. The consonance of the test procedure (Brannath and Bretz 2010) has also been ensured as described below.

The testing procedure in Figure 9-1 initially assigns the entire available significance level (at the final analysis 2.45%) equally to the two primary null hypotheses relating to the two doses (at the final analysis 1.225% for each). Key secondary endpoints for a dose are only tested after successful rejection of the primary null hypothesis for that dose. In that case, a slightly higher fraction of the local significance level is passed to the secondary CV composite endpoint than to the new onset of diabetes endpoint.

Note that if the primary endpoint for the 300 mg dose (null hypothesis H_{21}) is rejected 60% of the local significance level assigned to that null hypothesis is shifted to the primary endpoint for the 150 mg dose (null hypothesis H_{11}). In contrast, after rejecting H_{11} only 8% of the local significance level assigned to H_{11} would be shifted to H_{21}. This reflects the possibility that the 150 mg dose could potentially have the better safety profile of the two doses; hence, it would be desirable to demonstrate the efficacy of the 150 mg dose even after demonstrating the efficacy of the 300 mg dose. After the rejection of H_{11} 8% of the local significance level assigned to H_{11} is shifted to H_{21} in order to preserve the consonance of the test procedure; i.e. to avoid a situation in which the primary null hypothesis for the 300 mg would be rejected by Dunnett's test, but could not be rejected by the chosen closed testing procedure due to insufficient alpha being assigned to some intersection null hypotheses.

Figure 9-1 Closed testing procedure for primary and key secondary endpoints



H_{12} is the null hypothesis relating to the secondary CV endpoint for the 150 mg dose, H_{22} is the respective null hypothesis for the 300 mg dose. H_{13} is the null hypothesis relating to the new onset of diabetes endpoint for the 150 mg dose, H_{23} is the respective null hypothesis for the 300 mg dose. In the notation of Bretz, Maurer, Brannath and Posch, a weight of ε for an edge indicates an infinitesimally small weight. If a hypothesis (vertex) with such an outgoing edge is rejected and the vertex removed, no significance level is passed on along such an edge as long as there are other outgoing edges with positive weights. If after removal of another vertex only infinitesimal outgoing edges remain, then the algorithm of Bretz et al. turns them into edges with positive weights that sum to 1. In this specific procedure, this implies that no significance level is passed from the secondary null hypotheses of a dose to the primary null hypothesis of the other dose until both key secondary null hypotheses have been rejected. To ensure the sum of weights on all outgoing edges of a vertex is 1 when such edges are present, some edges are given a weight of 1 – ε. For any intersection hypothesis from the full closure that contains both H_{11} and H_{21}, a Dunnett test for H_{11} and H_{21} is performed at the full significance level for the respective analysis (at the final analysis 2.45%).

Two efficacy interim analyses, at which the trial could be stopped for demonstrated efficacy or one or both active arms could be stopped for futility will be performed respectively after 50% and 75% of the target number of 694 patients have experienced a primary endpoint. Futility criteria and the criteria other than purely formal statistical significance required for stopping the trial for demonstrated efficacy will be specified in the Data Monitoring Committee charter.

A fixed Bonferroni split of the one sided significance level will be used to account for the two efficacy interim analyses and the final analysis, with a significance level of 0.01% for the first and 0.04% for the second efficacy interim analysis. I.e. the closed testing procedure will be performed with a one-sided significance level of 0.01% at the first efficacy interim analysis, with a one-sided significance level of 0.04% at the second efficacy interim analysis and with a one-sided significance level of 2.45% at the final analysis. In this fashion the familywise type I error rate will be controlled at the overall (one-sided) significance level $\alpha = 2.5\%$.

The hazard ratios and their associated confidence intervals will be estimated by means of a (Cox 1972) proportional-hazards model stratified by time since index MI (< 6 months, ≥ 6 months) using treatment (canakinumab doses and placebo) as a factor in the model using (Peto 1972) exact method for handling ties. Kaplan-Meier plots will be presented to summarize the time to first event in the composite endpoint, by presenting the time-dependent cumulative frequency and percentage of patients who reach the primary composite endpoint by treatment group.

Should one of the two active arms be stopped due to safety reasons or futility, then thereafter the pre-specified testing procedure will be performed for the other arm treating all null hypotheses for the stopped arm as non-rejected. In such a case where one active arm is stopped, then additionally the target number of patients with a MACE that is still to be collected has to be adjusted. It will be reduced by 30%. The size of this reduction is based on the proportion of events assumed to be available for the non-stopped comparison during sample size calculations. Under the main scenario for sample size calculation, both active arms have a 23.9% relative hazard reduction; in that case the expected proportion of events for the comparison of one active arm versus placebo is $(1+0.761)/(1+0.761+0.761) \approx 0.7$ and 30% of events would be expected to occur on the other active arm. While it is not clear, whether there is any adjustment rule for determining the target number of patients with an event after stopping one trial arm that can be absolutely guaranteed to have no effect on the type I error rate, it is expected that the conservativeness of the testing strategy in this case will outweigh any such small effects.

9.4.3 Handling of missing values/censoring/discontinuations

Regarding time-to-event endpoints only observed events will be used in the analysis and in the primary analysis censoring of non-observed events will be assumed to be non-informative. Sensitivity analyses with respect to this assumption will be performed. Incomplete dates of events and censoring dates will be imputed as described below.

In the primary analysis, all patients, including those who discontinue study therapy due to lack of efficacy, adverse events or abnormal laboratory values will be followed until death or the end of the study. Information of patients discontinuing study drug or participation in trial visits will be collected whenever possible and will be used in the analysis. In patients who could not be followed up for primary outcome events, it is aimed to at least determine the vital status of the patients at the final visit.

The following rules will be applied separately for the composite MACE endpoint and for all its individual components. Patients who have not experienced the respective endpoint will be censored on the date of the last follow-up in the following way:

- for patients who die, the censoring date will be the date of death unless the patient withdrew his consent for the collection of follow-up information,
- for patients who attend a final visit during close out, the censoring date will be the final visit date,
- otherwise the censoring date will be based on the last visit at which the investigator reported that it was known whether the patient experienced any clinical events since the last visit (i.e. answer of “yes” or “no” to this question, not “unknown”. The last known date the patient was reported alive at that visit will be used, if the last known date the patient was alive is missing the date of the last visit at which it was known whether the patient experienced any clinical events since the last visit will be used.

Should the censoring date lie after the chosen analysis cut-off date, it will be set to the analysis cut-off date.

If the date of a MACE endpoint or of censoring is not known or is incomplete following all attempts to get an approximate date, a day will be imputed using the following algorithm:

- If only the month of the event is known, then the 15th day of this month will be imputed.
- If only the year of the event is known, then the 1st July will be imputed.
- If year, month and day are unknown, the randomization date will be imputed.
- If this imputation rule leads to a date before the randomization date or after a patient’s last study visit or after a patient’s death, but before the imputation the date could have been on one of these dates, then the date will be imputed as that date.

9.4.4 Supportive analyses

The components of the composite primary efficacy endpoint (CV death, fatal or non-fatal MI, fatal or stroke) will also be analyzed individually in order to evaluate their contributions to the overall treatment effect.

The primary endpoint will also be analyzed on the PPS. Additionally in an on-treatment analysis on the FAS patients will be considered censored at the latest one quarter year + 28

days (119 days) after the last study injection. Besides adjudicated endpoints investigator reported outcomes will also be analyzed.

Furthermore, pre-specified subgroup analyses will include age, sex, race, ethnicity, BMI, region, glycemic status, smoking status, baseline hsCRP level, LDL-C levels, SBP/DBP levels, statin, aspirin, gout and renal failure. Possible interactions between treatment and baseline variables will be evaluated with appropriate methods. Results will be presented graphically as forest plots. The objective of the subgroup analyses is to show the consistency of treatment effects across a wide variety of patient groups. Additional subgroup analyses will be considered and pre-specified prior to unblinding of trial database for final analysis. Additionally, the post-baseline subgroups of response in hsCRP response and target hsCRP levels achieved will be explored.

9.5 Analysis of key secondary and exploratory variables

Unless otherwise specified all time-to-event analyses will be based on events occurring during the double-blind treatment period (see Section 9.4).

9.5.1 Secondary variables

Key secondary efficacy variables

The following key secondary variables will be used in the analyses:

- Time to the first occurrence of an adjudication committee confirmed composite cardiovascular endpoint consisting of the components of the primary endpoint and hospitalization for unstable angina requiring unplanned revascularization
- Time to adjudication committee confirmed new onset of type 2 diabetes among those with pre-diabetes at randomization

The following hypotheses will be tested with respect to the key secondary variables for the canakinumab 150 mg dose versus placebo

- H_{12}: The hazard rate of first adjudication committee confirmed secondary composite CV endpoint in the canakinumab 150 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{13}: The hazard rate of new onset of diabetes for pre-diabetic patients in the canakinumab 150 mg dose group is greater than or equal to the hazard rate of the placebo group

Each null hypothesis is tested against the one-sided alternative that the hazard rate is smaller for the canakinumab 150 mg dose group than in the placebo group. The corresponding hypotheses for the comparison of the canakinumab 300 mg dose versus placebo are H_{22} for the secondary composite CV endpoint and H_{23} for the new onset of diabetes endpoint.

All key secondary efficacy variables will be analyzed on the FAS with a log-rank test stratified by time since index MI. The hazard ratios will be estimated using a Cox regression model stratified by time since index MI. Kaplan-Meier plots showing each treatment will be provided. The multiplicity adjustment used to protect the familywise type I error rate is shown in Figure 9-1.

The secondary efficacy variable corresponding to new onset diabetes in patients with pre-diabetes at randomization will be the time from randomization to the first of repeated FPG > 126 mg/dL or the first of repeated HbA1c ≥ 6.5% or start of new anti-diabetic concomitant medication(s) for glucose lowering purpose. Due to the discrete nature of the time points when new onset of type 2 diabetes can be determined, events identified at the same visit time point for different patients will be considered as tied events and (Peto 1972) exact method for handling ties will be used. This assumes that for each of these patients new onset of diabetes occurred at some time point since the previous visit, but that due to the impossibility of continuous monitoring of the patients the true order in which each of them progressed to diabetes is unknown (Allison 1995). For this endpoint, patients without new onset of diabetes will be considered censored at the time of their last laboratory assessment.

Other secondary efficacy variables

Although all-cause mortality is considered a very important secondary endpoint due to its importance as both an efficacy and safety outcome, it is not part of the pre-specified testing procedure for primary and key secondary endpoints, because given the expected number of deaths in the trial it would not have been possible to adequately power the key secondary mortality endpoint.

All-cause death and the composite of all-cause death, stroke or MI will be analyzed on the FAS with a log-rank test stratified by time since index MI. The hazard ratios will be estimated using a Cox regression model stratified by time since index MI. Kaplan-Meier plots showing each treatment will be provided. Patients who did not die will be considered censored at the last time they were reported to be alive.

Analysis of the washout period

Data from the double-blind treatment period and the washout period will be combined to assess to what extent canakinumab truly delayed progression to diabetes and to what extent it only masked diabetes during the double-blind treatment period. The analysis will take into account that masking of diabetes may have occurred in patients not diagnosed as diabetic during the core study that did not enter the washout period. A number of sensitivity analyses with a range of assumptions about these patients will be performed. These analyses will be specified in a detailed Statistical Analysis Plan prior to the first efficacy interim analysis.

Analysis of the Post-Stroke Functional Assessment Sub-Study

In line with the primary objective of the post-stroke functional assessment sub-study to evaluate canakinumab arms facilitates functional recovery from stroke, the primary endpoint for this sub-study is the modified Rankin scale assessment 90 days post-stroke. Further endpoints are the 30 day results of the modified Rankin scale assessment, the 30 and 90 day MFSI-SF and the 30 and 90 day SIS-16.

Analyses will be fully specified in a detailed Statistical Analysis Plan and will take into account that while patients were initially randomly assigned to treatments the subset of patients experiencing a stroke may represent a biased subset. The impact of the occurrence of fatal strokes in the main study on the results of the sub-study will also be considered.

9.5.2 Exploratory Efficacy variables

Exploratory time-to-event outcomes will be analyzed using Cox models including treatment with time since index MI as a stratification variable, along with Kaplan-Meier analyses. Exploratory continuous outcome variables (i.e. change from baseline of HbA1c, biomarkers, etc.) will be analyzed using both a repeated measures analysis of covariance adjusted for baseline value and time since index MI as a factor, as well as a descriptive analysis.

The following endpoints will be analyzed

- Time to other cardiovascular disorders with a known inflammatory component:
    - Time to first deep vein thrombosis/pulmonary embolism
    - Time to first supraventricular tachycardia/atrial fibrillation
    - Time to first stent thrombosis (probable or definite)
    - Time to first hospitalization or prolongation of hospitalization for heart failure
    - Time to first event of major coronary events composite (CHD death or MI)
    - Time to first event of total vascular events composite consisting of primary endpoint, hospitalization for unstable angina, or for any other non-coronary ischemic event (transient ischemic attack or limb ischemia), any revascularization procedure (coronary and non-coronary) and limb amputation
    - Time to first event of coronary revascularization procedures (PCI or CABG)
    - Time to first event of stroke by etiology
- It will be explored whether the early high induction dose regimen in 300 mg canakinumab arm has an impact on early (within 90 days of randomization) primary and secondary clinical cardiovascular events when compared to the placebo arm and to the 150 mg canakinumab arm with no early high, induction dose regimen.
- Time to nephropathy as assessed by urine albumin/creatinine ratio (≥ 30 mg/mmol) in patients with T2DM or pre-diabetes at baseline
- Glycemic control among those with type 2 diabetes at baseline defined by HbA1c and/or FPG or medical history and/or concomitant medications criteria in Section 4 (analyses will use baseline HbA1c, and baseline BMI as continuous covariates and the use of diabetic medications at baseline (yes/no) as a factor in the analysis models).
    - Time to failure of glycemic control defined as HbA1c ≥ 7.5% confirmed by a second HbA1c within 6 weeks in those patients that were diabetic at baseline with a baseline HbA1c < 7.0%
    - Change from baseline in HbA1c overall and by visit in all patients that were diabetic at baseline
- Change from baseline in biomarkers of cardiovascular and diabetes risk, including inflammatory biomarkers, glycemic control markers, β-cell function markers, FPG, and HbA1c including:
    - Achieved reductions from baseline in hsCRP
    - Target hsCRP levels achieved

9.5.3 Safety variables

Safety will be evaluated based on the safety set (SAF). The assessment of safety will be based primarily on the assessment of potential and identified risks defined in the safety profiling plan (SPP), the frequency of adverse events, laboratory abnormalities, and serious adverse events suspected by the investigators to be related to study treatments. Other safety data (like vital signs, ECG) will be summarized as appropriate.

Adverse events between informed consent and randomization

Adverse events between informed consent and randomization will be summarized by primary system organ class and preferred term. This summary will include events that would qualify as trial endpoints if they occurred after randomization, but which are to be reported as AEs prior to randomization.

Treatment emergent adverse events (AEs) excluding trial endpoints

The incidence of treatment emergent AEs (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) excluding trial endpoints will be summarized by primary system organ class (SOC), preferred term and also by severity and relationship to study treatment. If warranted, time to event analysis methods will be used. Standardized MedDRA Queries (SMQs) will also be employed. The MedDRA version used for reporting the study will be clearly identified.

If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

The number and percentage of patients reporting any AE during the double-blind period of the study will be summarized by primary system organ class, preferred term and treatment and also by SMQ and treatment.

Separate summaries will be provided for study drug related AEs, deaths, SAEs and, other significant AEs leading to discontinuation.

AEs of special interest

Frequencies of adjudicated immunological AEs (serious allergies/immunological events (e.g. immunological laboratory screen and anti-canakinumab antibodies), serious infections, and malignancies, whether newly detected or worsening of existing malignancies) will be reported.

Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (Hematology, Serum chemistry and Urinalysis).

Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test and treatment

group. Change from baseline will only be summarized for patients with both baseline and post baseline values.

In addition, shift tables by treatment group will be provided for all parameters (except for creatinine clearance, which will be calculated using the MDRD formula) in order to compare a patient's baseline laboratory evaluation relative to all post-baseline values.

The frequency and percentage of patients with clinically notable laboratory results after baseline will be tabulated.

Liver safety

The following analyses will be performed:

- The liver-related events meeting specified criteria standard table will be used to provide the number and percentage of patients having aspartate transaminase (AST), alanine transaminase (ALT) > 3, 5, 8, 10 x ULN or total bilirubin (TBL) >1.5, 2 x ULN or alkaline phosphatase (AP) > 2, 3 x ULN. The number and percentage of potential Hy's Law cases will be presented by treatment group. Potential Hy's Law cases are defined as those patients with AST or ALT >3xULN and TBL >2xULN and AP <2xULN at the same lab measurement.
- A cross-tabulation of baseline and worst post-baseline values by below, within and above normal range categories will be provided. Shift tables will be provided for the parameters AST, ALT, TBL and AP. These summaries will be presented by laboratory test and treatment group.
- Standard laboratory tables will be produced as for all other laboratory parameters.
- The narrow and broad "Possible drug related hepatic disorders – comprehensive search" SMQ and the corresponding lower level SMQs will be presented including the respective preferred term frequencies covered under the SMQs.
- The overall SMQ/preferred term table will be used to provide the number and percentage of patients with hepatic disorders.
- eDISH (electronic Drug-Induced Serious Hepatotoxicity) plots will be provided representing the entire study population.
- Narratives for any patients discontinued due to liver function abnormalities will be prepared.

Vital signs

Descriptive summary statistics of vital sign variables for the change from baseline to each post baseline visit will be presented. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values.

ECG

Based on a standard 12-lead ECG, any new or worsening clinically relevant findings will be recorded as AEs except for ECG changes constituting study endpoints. Therefore, no separate presentation of ECG findings is foreseen

9.5.4 Resource utilization

Analyses of healthcare resource utilization data will be specified separately.

9.5.5 Patient Reported Outcomes

Exploratory efficacy patient reported outcome variables including those related to tiredness, physical function, performance function and health status, will be generated from the Modified Rankin Scale, MGSI-SF, SF-36, SIS-16, EQ-5D, Heath State Classification, and Visual Analogue Scale. These will be analyzed using a repeated measures analysis of covariance with baseline levels as a covariate and summarized descriptively.

EQ-5D

Health state classification will be converted to a score (during data analysis stage) according to a list provided. This list has 243 values for all possible EuroQoL health status. For example, a health state of 11111 will have a score of 1.00 and a health status of 12132 will have a score of 0.09.

The analysis will involve the estimation of weighted indices over time for patients in each treatment group. The weighted indices will be displayed graphically along with the respective treatment means. The change from baseline in VAS scores will also be summarized using descriptive statistics.

Analysis based on EQ-5D data will be reported separately, and will not be part of the clinical study report.

9.5.6 Pharmacokinetics

A mixed effects modeling approach may be used to characterize the PK of canakinumab and it's binding to IL-1β. The relationship between population parameters such as CL/F and covariates such as dose, age, and weight may be investigated using graphical methods and simple regression models. Quality of individual fits to the dataset will be assessed, and individual model parameters (post-hoc estimates) may be obtained for each patient. Alternatively, in case the population based modeling may not be feasible, the analysis will be limited to the methodology based on predictive check, where the measures of systemic drug exposure (pre-dose trough levels) and biomarker response (IL-1 β) will be plotted against the data collected in previous trials.

9.5.7 Pharmacogenetics/pharmacogenomics

Pharmacogenetics

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests (chi-square tests, ANCOVAs, linear and logistic regression) are used for the analyses. Additional data, from subsequent clinical trials, are often needed to confirm associations. Alternatively, if the numbers of patients enrolled in the study are too small to complete proper statistical analyses,

these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

Pharmacogenomics

For pharmacogenomics, messenger RNA (mRNA) will be extracted from blood samples. mRNA will be analyzed for gene expression using gene expression microarrays such as Affymetrix microarray technology and/or quantitative RT-PCR. Quality control of all individual RNA samples and expression data will be conducted. The gene expression data will be analyzed using several different algorithms including various clustering analysis algorithms, ANOVA correlation analysis, and different filtering strategies based on magnitude and statistical significance of differences of gene expression.

9.5.8 Biomarkers

Biomarkers associated with cardiovascular disease will be measured. These include IL-1ra, IL-6, IL-18, leptin, adiponectin, TNFα, PAI-1 and fibrinogen

Descriptive statistics will be provided by treatment group for the FAS including geometric mean and 95% confidence intervals for the geometric mean.

9.5.9 PK/PD

Refer to Section 9.5.6

9.6 Sample size calculation

Expected event rates in a secondary prevention trial in patients with prior MI

In spite of differences in eligibility criteria and outcome definitions, several recent trials provide useful information on the expected rates of the endpoint in the proposed trial, and support the focus on hard endpoints. The ARISE trial (Tardif et al. 2008) randomized 6,144 patients with recent acute coronary syndrome (between 14 and 365 days before enrollment) to succinobucol vs. placebo and followed them for an average of 2 years. The observed incidence on the composite endpoint of cardiovascular death, MI, stroke or cardiac arrest corresponds to an incidence rate of 5.1 events per 100 person-years.

The PROVE-IT TIMI-22 trial (Cannon et al. 2004) provides an additional estimate of event rates in post-acute coronary syndrome patients (71% post MI), randomized within less than 10 days post index event. Over an average follow-up of 2 years, the 2,099 patients in that trial randomized to receive 80 mg of atorvastatin daily had a cumulative incidence of myocardial infarction or death from coronary heart disease of 7.2%. This corresponds to an incidence rate of 3.7 events per 100 person-years. The addition of stroke and other cardiovascular deaths to this endpoint might be expected to increase this rate to over 4 events per 100 person-years.

The WIZARD trial (O'Connor et al. 2003) provides an additional estimate of event rates based on somewhat different eligibility criteria. That trial randomized individuals with a history of myocardial infarction anytime in the past who also had a C pneumoniae IgG titer of 1:16 or more to azithromycin or placebo and followed these people for an average of 14 months. In 7,722 patients followed for the endpoint of recurrent myocardial infarction or

death a total of 600 experienced the event with a median follow up of 14 months, corresponding to an incidence rate of 6.7 events per 100 person-years.

Levels of hsCRP in patients with prior myocardial infarction are powerful predictors of subsequent events. Rates of recurrent events are 30% to 60% higher in patients with hsCRP≥2 mg/L relative to lower levels, regardless of the intensity of statin treatment (Ridker et al. 1998). While aggressive lipid-lowering with statins reduces levels of hsCRP, elevations remain common in post-MI patients. Specifically, in the PROVE-IT TIMI-22 trial, 43% of patients randomized to 80 mg atorvastatin daily had on-treatment levels of hsCRP ≥ 2 mg/L (Ridker et al. 2005). A similar prevalence of elevated hsCRP was observed in patients treated with 80 mg simvastatin daily in the Aggrastat-to-Zocor trial (Morrow et al. 2006). In the primary prevention setting of the JUPITER trial (Ridker et al. 2008), 20 mg of rosuvastatin substantially reduced levels of hsCRP from a baseline median of 3.2 mg/L, but on-treatment median levels in the active treatment group remained above 2 mg/L at all follow-up visits.

The event rates from these trials that have included individuals with prior myocardial infarction, with the additional consideration of the increased MACE rate associated with an elevated level of hsCRP, appear to support an estimate of the expected MACE rate of 3.25 to 4 per 100 person-years in the placebo group. This range already takes into consideration that full-dose statin therapy will most likely be used by such patients. The expected risk during the first year of the trial is expected to be higher for patients randomized within 30 days to 6 months of their index MI, than for patients randomized longer after their index MI.

Needed number of patients with primary endpoints and Sample size

As shown in Table 9-1 694 patients across all three trial arms with an observed major cardiovascular disease event (MACE) provide 90% power for demonstrating the superiority of at least one dose of canakinumab over placebo using the closed testing described in Section 9.4 Analysis of the primary variable (s). at the one-sided 2.45% level available for the final analysis if both doses have a true 23.9% net relative hazard reduction compared to placebo for MACEs after discounting for discontinuations of treatment. This power remains close to 80% if one of the two arms is less effective and only has a relative hazard reduction of 15%.

Table 9-1 Power at the final analysis for 694 patients with a MACE

Relative Risk Reduction 300 mg (%)	Relative Risk Reduction 150 mg (%)	**Power to have at least one dose significant**	Power for 300 mg dose (%)	Power for 150 mg dose (%)	Power to have both doses significant
23.9	23.9	**90**	78	81	69
23.9	20	**85**	78	64	57
23.9	15	**79**	77	39	36
23.9	10	**77**	76	19	18
23.9	5	**75**	75	7	7
23.9	0	**74**	74	NA	NA
0	23.9	**74**	NA	74	NA
20	20	**85**	59	62	46
15	15	**48**	33	35	20

Relative Risk Reduction 300 mg (%)	Relative Risk Reduction 150 mg (%)	**Power to have at least one dose significant**	Power for 300 mg dose (%)	Power for 150 mg dose (%)	Power to have both doses significant

Power results are based on 500,000 simulated trials per scenario. Only results for primary endpoints were simulated, therefore the actual power will be slightly higher as significant key secondary endpoints for one dose may make more alpha available for the primary endpoint of the other dose.

All simulations were performed in SAS 9.2 (TS1M0) on an AIX 6.1 platform.

Depending on the exact distribution of endpoints across the three trial arms at least one canakinumab arm needs to achieve a relative hazard reduction compared to placebo of approximately 18 to 19% in order to result in a significant result at the final analysis.

To estimate the sample size and follow-up time required to achieve this number of patients with events, a piecewise exponential distribution for the time to MACE variable with hazard rates in the placebo arm of 4.5% for the first year and 3% yearly for subsequent years was assumed. These hazard rates correspond to a cumulative incidence rate of 4.4% at the end of the first year, and 7.2% at the end of the second year. Furthermore a patient accrual period of 1.5 years, a total study length (including the patient accrual period) of 4.5 years and a cumulative rate of patients lost to follow up of 15% were assumed. Under these assumptions, a sample size of 7,302 randomized patients (in 1:1:1 allocation ratio to canakinumab 300 mg dose, canakinumab 150 mg dose and placebo) is expected to be sufficient to accrue the planned number of patients with a MACE.

In order to achieve the planned number of events and preserve the target power of the study the event rate of the primary endpoint will be monitored in a blinded fashion so that adjustments can be made to the number of patients to be randomized and/or the duration of follow-up.

9.7 Power for analysis of key secondary variables

Secondary CV composite endpoint and new onset of diabetes

The majority of events for the key secondary composite endpoint of MACE or hospitalization due to unstable angina requiring revascularization are expected to come from its MACE component. It will be assumed that the additional component will constitute 15% of the composite endpoint and that the relative hazard reduction is 23.9% for both MACE and hospitalization due to unstable angina requiring revascularization.

Because the inclusion criteria for this trial are such that the pre-diabetic patients are not specifically selected to have elevated post-load plasma glucose concentrations, event rates for new onset of type II diabetes may be expected to be somewhat lower than in the Diabetes Prevention Program (Diabetes Prevention Program Research Group 2002). In that trial they were 11.0 per 100 person-years in the placebo arm, 7.8 per 100 person-years in the metformin group and 4.8 per 100 person years in the life-style group. Additionally the criteria defining the new onset of diabetes endpoint differ adding further uncertainty about event rates. It will be assumed that the event rate in the control arm is 2/3 of that observed in DPP and that canakinumab is as effective as metformin with a 31% relative hazard reduction versus control in preventing or delaying new onset of diabetes. If 35% of the 7,302 patients to be randomized are pre-diabetic and follow-up for diabetes is on average 3¼ years, then on average 343 new

onsets of diabetes would be expected to be available for comparing one canakinumab arm versus placebo.

Under these assumptions the power for the secondary composite CV endpoint for the 150 mg dose is 80% and for the 300 mg dose 71% at the final analysis using the pre-specified testing procedure. Correspondingly, the power using the pre-specified testing procedure for the new onset of diabetes endpoint would be 74% for the 150 mg dose and 64% for the 300 mg dose. Should the rate of new onset of diabetes in the control arm be higher, then the power for the new onset of diabetes endpoint would be higher; should the rate of new onset of diabetes in the control arm be lower, then the power would be lower. Similarly, should the hospitalization due to unstable angina requiring revascularization component add more patients with events to the secondary composite CV endpoint than assumed, the power for that endpoint would be higher as long as the respective canakinumab dose has the assumed effect on the unstable angina requiring revascularization component of the composite.

The lower power for the key secondary endpoints of the 300 mg dose as opposed to those for the 150 mg dose is a consequence the chosen asymmetric testing procedure, which prioritizes the secondary endpoints for the 150 mg dose once the 150 mg dose has been shown to be efficacious, but tries to establish the efficacy of the 150 mg dose even after the 300 mg dose has been shown to be efficacious as explained in Section 9.4.2.

9.8 Interim analyses

Interim analyses of efficacy, futility and safety will be carried out during the study. Two interim analyses of efficacy will be performed when about 50% of the target number of primary cardiovascular events have been accumulated and the second one when 75% of the planned number of events are available. Criteria for the interim and final analyses will be determined using a fixed Bonferroni split of the alpha allocated to the interim analyses and to the final analyses in order to protect the overall one-sided familywise type I error rate across all analyses at 2.5%. The fixed total one-sided alpha allocated to both interim analyses of efficacy combined is 0.05%. Of this 0.01% is allocated to the first efficacy interim analysis and 0.04% allocated to the second efficacy interim analysis. The one-sided significance level for the final analysis is thus 2.45%.

Interim analyses for futility will be conducted simultaneously with the two analyses of efficacy. It should be noted that the efficacy criteria are not modified to “buy back” alpha based upon the presence of futility boundaries; this conservative approach ensures that the familywise type I error rate of the study is protected.

Full details on boundaries and stopping rules will be pre-specified in the Charter of the Data Monitoring Committee (DMC). Timing and number of safety analyses will also be specified in DMC charter.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local

regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

This study includes an optional pharmacogenetic/pharmacogenomics component which requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents this option to the patient. The process for obtaining informed consent should be exactly the same as described above for the main informed consent.

Declining to participate in this pharmacogenetic/ pharmacogenomics assessment will in no way affect the patient's ability to participate in the main research study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or ethics committee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be submitted for publication and posted in a publicly accessible database of clinical study results regardless of study outcome.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

12 References

References are available on request.

Internal Reference Section

Investigator's Brochure, Edition 7 dated 19 January 2010

External Reference Section

Brannath W, Bretz F (2010) Shortcuts for locally consonant closed test procedures. J American Statistical Association ; 105(490),: 660-9.

Bretz F, Maurer W, Brannath W, et al (2009 A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine; 28(4): 586-604.

Cannon CP, Braunwald E, McCabe CH, et al (2004) Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators : Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. NEJM; 350:1495-504.

Cox DR (1972) Regression models and life-tables (with discussion). J. R. Statist. Soc, B; 34:187-220.

Diabetes Prevention Program Research Group (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. NEJM; 346:393-403.

Dinarello C, Ikejima T, Warner SJC, et al (1987) Interleukin 1 induces interleukin 1, I. Induction of circulating interkeukin 1in rabbits in vivo and in human mono nuclear cells in vitro. J. Immunol; 139: 1902-1910.

Duewell P, Kono H, Rayner KJ, et al (2010) NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature; 464(7293):1357-61.

Dunnett CW (1955) A multiple comparison procedure for comparing several treatments with a control. J American Statistical Association; 50:1096-1121.

European Commission : Enterprise and Industry Directorate-General (2006) Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use.. Brussels ENTR/CT 3 Revision 2.

European Society of Hypertension (2003) European Society of Cardiology guidelines for the management of arterial hypertension. Journal of Hypertension; 21:1011-1053.

Hochberg Y (1988) A sharper Bonferroni procedure for multiple tests of significance. Biometrika; 75:800-2.

Kaptoge S, Di Angeloantonio E, Lowe G et al Emerging Risk Factors Collaboration (2010) C-reactive protein concentration and risk of coronary heart disease, stroke and mortality: an individual meta-analysis. Lancet; 375:132-140.

Lan G, DeMets D (1983) Discrete sequential boundaries for clinical trials. Biometrika 70(3):659-663.

Little RR (2010) Consensus Statement on the Worldwide Standardization of HbA1c (Internet) Available from <http://www.ngsp.org/contact.asp> (Accessed 22 September 2010)

Mancia G, Laurent S, Agabiti-Rosei E et al (2009) Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertension; 27: 1-38.

McMurray JJ, Kjekshus J, Gullestad Let al (2009) Effects of statin therapy according to plasma high-sensitivity C- reactive protein concentration in the controlled rosuvastatin multinational trial in heart failure (CORONA), Circulation; 120: 2188-2196.

Morrow DA, de Lemos JA, Sabatine MS, et al (2006) Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor trial. Circulation; 114: 281-288.

O'Connor CM, Dunne MW, Pfeffer MA, et al (2003) Azithromycin for the Secondary Prevention of Coronary Heart Disease Events: The WIZARD Study: A Randomized Controlled Trial. JAMA; 290(11):1459-1466.

Peto R (1972) Discussion on Professor Cox's Paper. J. R. Statist. Soc., B; 34:205-207.

Ridker PM, Danielson E, Fonseca FA, et al (2008) Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. NEJM; 359:2195-2207.

Ridker PM, Danielson E, Fonseca FA, et al (2009) Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet; 373:1175-82.

Ridker PM, Cannon CP, Morrow D, et al (2005) C-Reactive Protein Levels and Outcomes after Statin Therapy, NEJM; 352:20-8.

Ridker PM, Rifai N, Clearfield M, et al (2001) Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events, NEJM; 344:1959-1965.

Ridker PM, Rifai N, Pfeffer MA, et al (1998) Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. Circulation; 98:839-44.

Tardif J-C, McMurray JJV, Klug E et al (2008) Effects of succinobucol (AGI-1067) after an acute coronary syndrome: a randomized, double-blind, placebo-controlled trial. Lancet; 371: 1761–8.

Thygesen, K, Alpert, JS, White, HD et al (2007). Universal Definition of Myocardial Infarction. Circulation; 116:2634-2653.

Warner SJC, Auger KR, and Libby P (1987a). Human interleukin 1 induces interleukin 1 gene expression in human vascular smooth muscle cells. J. Exp. Med; 165: 1316-1331.

Warner SJC, Auger KR, and Libby P (1987b) Human interleukin 1 induces interleukin 1. II. Recombinant human interkeukin 1 induces interleukin 1 production by adult human vascular endothelial cells. J. Immunol; 139: 1911-1917.

Book references

Allison PD (1995) Survival analysis using the SAS® System: A Practical Approach, Cary, NC: SAS Institute Inc.

Chou's Electrocardiography in Clinical Practice; Surawicz, B, Knilans, T; Ed. 5th Edition. (2001). Saunders Publishing. Literature available on request.

13 Appendix 1: Clinically notable laboratory values and vital signs

Laboratory notable range deviations will be provided in the investigator binder.

Vital sign notable range deviations

VITAL SIGNS		NOTABLE ABNORMALITIES
Pulse (beats/min)		either ≥120 + increase ≥25* or >130 either ≤50 + decrease ≥30* or < 40
Blood pressure (mmHg)	systolic	either ≥180 + increase ≥30* or > 200 either ≤90 + decrease ≥30* or < 75
	diastolic	either ≥105 + increase ≥20* or > 115 either ≤50 + decrease ≥20* or < 40
Weight		a weight change of > 10% during the study

*Refers to post-baseline value as compared to baseline value

14 Appendix 2 PK / PD/ IG Blood Collection Log

Table 14-1 PK / PD Blood Collection Log

Visit	Month	PK(pre-dose)			PD		IG	
		Canakinumab			IL-1β			
		PK Collection #	Sample #	mL	Sample #	mL	Sample #	mL
2	Baseline	1	1	2	101	3	201	2
7	Month 12	2	2	2	102	3	202	2
11	Month 24	3	3	2	103	3	203	2
EOS		4	4	2	104	3	204	2
Unscheduled Visit			1001, 1002, 1003,	2	1101, 1102, 1103,	3	1201, 1202, 1203	2

15 Appendix 3 Study Endpoint Definitions

15.1 Definition of Cardiovascular Death

Cardiovascular death includes sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to stroke, and death due to other cardiovascular causes.

Sudden cardiac death: A sudden death that occurs in a previously stable patient who does not have a prior terminal condition, such as malignancy not in remission or end-stage chronic lung disease.

Established sudden cardiac death includes the following deaths:

Witnessed and instantaneous without new or worsening symptoms.

Witnessed within 60 minutes of new or worsening symptoms.

Witnessed and attributed to an identified arrhythmia (e.g., captured on ECG recording or witnessed on a monitor by either a medic or paramedic or unwitnessed but found on implantable cardioverter-defibrillator review).

After unsuccessful resuscitation from cardiac arrest

After successfully resuscitated from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac arrest Syndrome)

Unwitnessed death without other cause of death

General Considerations

A patient seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as an "Unwitnessed Death." Typical scenarios include

• Patient well the previous day but found dead in bed the next day

• Patient found dead at home on the couch with the television on

Deaths for which there is no information beyond "Patient found dead at home" may be classified as "Undetermined Cause of Death"

Death due to Acute Myocardial Infarction (AMI): refers to a death within 30 days after a myocardial infarction (MI) related to consequences seen immediately after the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period), they should be designated by the immediate cause. The acute myocardial infarction should be verified either by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus, and there should be no conclusive evidence of another cause of death.

Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of

cardiac biomarkers in the blood should be considered death due to acute myocardial infarction.

If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

Death resulting from a procedure to treat myocardial ischemia or to treat a complication resulting from myocardial infarction should also be considered death due to acute MI.

Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be classified as death due to other cardiovascular cause.

Death due to Heart Failure or Cardiogenic Shock: refers to death occurring in the context of clinically worsening symptoms and/or signs of heart without evidence of another cause of death.

Death due to Heart Failure or Cardiogenic shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.

New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

- New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure
- Heart failure symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema
- Confinement to bed predominantly due to heart failure symptoms
- Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure
- Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin *or*
- Oliguria (urine output < 30 mL/hour) *or*
- Altered sensorium *or*
- Cardiac index < 2.2 L/min/m2

Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

Death due to Stroke (intracranial hemorrhage or non-hemorrhagic stroke): refers to death occurring up to 30 days after a suspected stroke based on clinical signs and symptoms as well as neuroimaging and/or autopsy, and where there is no conclusive evidence of another cause of death.

Death due to Other Cardiovascular Causes: refers to death due to a cardiovascular cause not
included in the above categories (e.g. dysrhythmia, pulmonary embolism, cardiovascular intervention, aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or non-surgical revascularization, even if "non-cardiovascular" in nature, should be classified as cardiovascular deaths.

Death of Undetermined Cause (presumed cardiovascular) :

All deaths not attributed to the categories of Cardiovascular Death or to a Non-cardiovascular cause are considered presumed cardiovascular deaths.

15.2 Non-cardiovascular death

Non-Cardiovascular death is defined as any death not covered by cardiac death or vascular death and is categorized as follows:

Pulmonary causes

Renal causes

Gastrointestinal causes

Infection (including sepsis)

Non-infectious causes

Malignancy

Accident/Trauma

Suicide

Non-cardiovascular system organ failure (e.g. Hepatic)

Hemorrhage, not intracranial

Other. Please specify.

15.3 Definition of Non-fatal Myocardial Infarction

Acute Myocardial Infarction : the term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI.

Spontaneous MI : Detection of rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia
- ECG changes indicative of new ischemia (new ST-T changes or new LBBB)*
- Development of pathological Q waves in the ECG**
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

- *ECG manifestation of acute myocardial ischemia (in the absence of LVH and LBBB):
- ST Elevation - New ST elevation at the J-point in two contiguous leads with the cut-off points:
- ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
- ST depression and T-wave changes – New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R waves or R/S ratio >1.
- **Pathological Q waves:
  1. Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
  2. Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 an any two leads of a contiguous lead grouping (I, aVL, V6, V4-V6, II, III, aVF).

Percutaneous Coronary Intervention (PCI) related Myocardial Infarct ; For PCI in patients with normal baseline troponin values elevations of cardiac biomarkers above the 99th percentile URL within 24 hours of the procedure are indicative of peri-procedural myocardial necrosis. By convention increases of biomarkers greater than 3 x 99th percentile URL are consistent with PCI related myocardial infarction.

- If the cardiac biomarker is elevated prior to PCI a ≥ 20% increase of the value in that second cardiac biomarker within 24 hours of the PCI and documentation that cardiac biomarkers were decreasing (two samples at least 6 hours apart) prior to the suspected recurrent MI is also consistent with PCI related MI.
- Symptoms of cardiac ischemia are not required
- CABG related Myocardial Infarct : For CABG in patients with normal baseline troponin, elevations of cardiac biomarkers above 5 times the 99th percentile of the normal reference range during the first 72 hours after CABG, when associated with

EITHER

New pathological Q waves in at least 2 contiguous leads on the ECG that persist through 30days or new LBBB

OR

Angiographically documented new graft or native coronary artery occlusion

OR

Imaging evidence of new loss of viable myocardium

Is consistent with CABG related Myocardial Infarct.

- If the cardiac biomarker is elevated prior to CABG a ≥ 20% increase of the value in the second cardiac biomarker within 72 hours of CABG AND documentation that the cardiac biomarkers were decreasing (2 samples at least 6 hours apart) prior to the suspected recurrent MI plus either new pathological Q waves in at least 2 contiguous leads on the ECG or new LBBB, angiographically documented new graft or native artery occlusion or

imaging evidence or new loss of viable myocardium is consistent with a peri-procedural myocardial infarct after CABG.

- Symptoms of cardiac ischemia are not required.

Criteria for Prior Myocardial Infarction : Any of the following criteria meets the diagnosis for prior myocardial infarction:

- Development of new pathological Q waves with or without symptoms
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract in the absence of a non-ischemic cause
- Pathological findings of a healed or healing myocardial infarction

ECG changes associated with prior Myocardial Infarction:

- Any Q wave in leads V2-V3 $\geq$ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave $\geq$ 0.03 seconds and $\geq$ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6, V4-V6, II, III, and aVF)
- R-wave $\geq$ 0.04 seconds in V1-V2 and R/S $\geq$ 1 with a concordant positive T-wave in the absence of a conduction defect

Criterion for Reinfarction : In patients where recurrent MI is suspected from clinical signs or symptoms following the initial infarction, an immediate measurement of the employed cardiac biomarker is recommended. A second sample should be obtained 3-6 hours later. Recurrent infarction is diagnosed if there is a $\geq$ 20% increase of the value in the second sample. This value should exceed the 99th percentile URL. However if cardiac biomarkers are elevated prior to the suspected new MI, there must also be documentation of decreasing values (two samples at least 6 hours apart) prior to the suspected new MI. If the values are falling criteria for reinfarction by further measurement of biomarkers together with features of the ECG or imaging can be applied.

ECG diagnosis of reinfarction following the initial infarction : may be confounded by the initial evolutionary ECG changes. Reinfarction should be considered when the ST elevation $\geq$ 0.1 mV reoccurs in an inpatient having a lesser degree of ST elevation or new pathognomonic Q-waves, in at least two contiguous leads, particularly when associated with ischemic symptoms for 10 minutes or longer, The re-evaluation of the ST segment can, however also be seen in threatening myocardial rupture and should lead to additional diagnostic work-up. ST depression or LBBB on their own should not be considered valid criteria for Myocardial Infarction.

If biomarkers are increasing or peak is not reached then there is insufficient data to diagnose recurrent MI.

Clinical Classification of different types of Myocardial Infarction :For each MI identified a Type of MI will be assigned using the following guidelines:

- Type 1 – Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring or dissection.
- Type 2 – MI secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, anemia, hypotension, coronary embolism, arrhythmias, hypertension or hypotension.

- Type 3 –Sudden unexpected cardiac death including cardiac arrest, often with symptoms suggestive of myocardial ischemia accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood.
- Type 4a –MI associated with PCI.
- Type 4b –MI associated with stent thrombosis as documented by autopsy or angiography.
- Type 5 –MI associated with CABG.

Silent MI

The following criteria will be used by the central ECG reading vendor to define interval "silent" (no clinical symptoms or signs) MI between baseline and yearly ECGs:

Criteria for MI (Surawcz, Ed : Chou's Electrocardiography in Clinical Practice, 5th Edition, 2001).

Myocardial infarctions are reported only on the basis of pathologic Q waves. Pathologic Q waves are defined as Q wave duration > 40ms **and** Q/R ratio = 1/3.

Any Q wave in V1 or V2 that is followed by an R wave should be considered abnormal.

When pathologic Q waves (i.e., myocardial infarction) are present, ST elevation or T wave inversion may be used to classify the infraction as New or Acute. However, ST elevation or T wave inversion in the absence of pathologic Q waves are not sufficient criteria for diagnosis of myocardial infarction.

- **Anterolateral MI** - Pathologic Q waves in leads V3-V6.
- **Anterior MI** - Pathologic Q waves in V3 and V4.
- **Anteroseptal MI** - Pathologic Q waves or QS in leads V1-V4.
- **Extensive Anterior MI** - Pathologic Q waves in leads I, aVL, and V1-V6.
- **High lateral MI** - Pathologic Q waves in leads I and aVL.
- **Inferior MI** - Pathologic Q waves or QS in at least two of the inferior leads: aVF, III, II.
- **Lateral MI** - Pathologic Q waves in leads I, aVL, and V5-V6.
- **Septal MI** - Pathologic Q waves or QS in leads V1-V2, (V3). **In the presence of LAHB or LVH a Q or QS in V3 is required.**
- **Posterior MI** - Initial R wave duration 40 ms in V1 or V2, and R > S and upright T wave; Inferior or Lateral MI are usually also present.

New MI

These criteria for MI are more stringent than the Expert Consensus Document criteria, requiring Q waves to be $\geq$ 0.04 sec in duration and an R/S ratio $\geq$ 1/3. These criteria (drawn from the cardiology literature) are designed to minimize the false positive detection of MIs due to very small physiologic Q waves in the inferior and anterolateral leads.

15.4 Definition of Stroke

Stroke: is defined as the rapid onset of a new persistent neurological deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g. tumor, trauma, infection). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Non-fatal strokes will be classified as ischemic, hemorrhagic or unknown.

For the diagnosis of Stroke, the following 4 criteria should be fulfilled:

1. Rapid onset* of a focal/global neurological deficit with at least one of the following:
   Change in level of consciousness
   Hemiplegia
   Hemiparesis
   Numbness or sensory loss affecting one side of the body
   Dysphasia/aphasia
   Hemianopsia
   Amaurosis Fugax
   Other new neurological sign/symptom(s) consistent with stroke
   *if the mode of onset is uncertain, a diagnosis of stroke may be made provided that there are no plausible non-stroke causes for the clinical presentation.
2. Duration of a focal/global neurological deficit:
   ≥ 24 hours
   OR
   < 24 hours if:
   This is because of at least one of the following interventions
Pharmacologic (i.e. Thrombolytic drug administration)
Non-pharmacologic (i.e. Neurointerventional procedure (e.g. Intracranial angioplasty)
   OR
3. Available brain imaging clearly documents a new hemorrhage infarct
   OR
4. The neurological deficit results in death.

No other readily identifiable non-stroke cause for the clinical presentation (e.g. Brain tumor, trauma, infection, hypoglycemia, peripheral lesion)

Confirmation of the diagnosis by at least on of the following:

Neurology or neurosurgical specialist

Brain imaging procedure (at least one of the following):

i. CT scan

ii. MRI scan

iii. Cerebral vessel angiography

Lumbar puncture (i.e. Spinal fluid analysis diagnostic of intracranial hemorrhage)

If the acute focal signs represent a worsening of a previous deficit, these signs must have either:

- Persisted for more than one week or
- Persisted for more than 24 hours and were accompanied by an appropriate new MRI or CT scan finding

Strokes are sub-classified as follows:

Ischemic (non-hemorrhagic): A stroke caused by an arterial occlusion due to either a thrombotic) e.g. Large vessel disease/atherosclerotic or small vessel/lacunar) or embolic etiology

Hemorrhagic: A stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular), ischemic strokes with hemorrhagic transformation (i.e.; no evidence or hemorrhage on an initial imaging study but appearance on a subsequent scan), subdural hematoma*, and primary subarachnoid hemorrhage.

*All subdural hematomas that develop during the clinical trial : should be recorded and classified as either traumatic versus non traumatic.

Unknown: the stroke type could not be determined by imaging or other means (e.g. Lumbar puncture, neurosurgery, or autopsy) or no imaging was performed

Stroke Disability

Stroke disability can be classified using an adaptation of the modified Rankin Scale as follows:

0: No symptoms at all

1: No significant disability despite symptoms; able to carry out all usual duties and activities

2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3 : Moderate disability; requiring some help, but able to walk without assistance

4 : Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5. Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6. Dead

15.5 Definition of Stent Thrombosis

1. Stent Thrombosis: Timing:

Type	Timing
Acute stent thrombosis*	0 to 24 hours after stent implantation
Subacute stent thrombosis	> 24 hours to 30 days after stent implantation
Late stent thrombosis†	> 30 days to 1 year after stent implantation
Very late stent thrombosis†	> 1 year after stent implantation

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified above. Time 0 is defined as the time point after the guiding catheter has been removed and the patient has left the catheterization laboratory.

***Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 to 30 days) will be used in the remainder of this document.**

†Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.

2. ARC Definitions of Definite, *Probable and Possible Stent Thrombosis

Definite Stent Thrombosis

Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation:

a. Angiographic confirmation of stent thrombosis : The presence of a thrombus that originates in the stent or in the segment 5mm proximal or distal to the stent and presence of at least 1 of the following within a 48 hour time window:

1. Acute onset of ischemic symptoms at rest

2. New ischemic ECG changes that suggest acute ischemia

3. Typical rise and fall in cardiac biomarkers

4. Non-occlusive thrombus :

a. Intracoronary thrombus is defined as a (spherical, ovoid or irregular) non calcified filling defector lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections or persistence or contrast material within the lumen, or a visible embolization or intraluminal material downstream.

5. Occlusive thrombus

a. TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

b. Pathological confirmation of stent thrombosis. Evidence of recent thrombosis within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable Stent Thrombosis

Clinical definition of probable stent stenosis is considered to have occurred after intracoronary stenting in the following cases:

a. Any unexplained death within the first 30 days

b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other cause.

15.6 Definition of Unstable Angina Requiring Unplanned Revascularization

Unstable Angina requiring Unplanned Revascularization is defined as :

No elevation in cardiac biomarkers

and

Clinical presentation (one of the following) with cardiac symptoms lasting ≥10 minutes and considered to be myocardial ischemia on final diagnosis

- Rest angina or
- New onset (<2 months) severe angina (CCS* classification severity ≥ III) or
- Increasing angina (in intensity, duration and/or frequency) with an increase in severity of at least 1 CCS class to at least CCS III

and

Severe recurrent ischemia requiring urgent revascularization: as defined by an episode of angina prompting the performance of coronary revascularization on the index hospitalization

or

An episode of recurrent angina after discharge that resulted in re-hospitalization

during which coronary revascularization was performed.

and

At least one of the following:

- New or worsening ST or T segment changes on ECG. ECG changes should satisfy the following criteria for AMI in the absence of LVH and LBBB
- ST Elevation - New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
- ST depression and T-wave changes – New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.
- Evidence of ischemia on stress testing with cardiac imaging.
- Evidence of ischemia on stress testing without cardiac imaging but with angiographic evidence of ≥ 70% lesion, and/or thrombus in the epicardial coronary artery or initiation/increased dosing of anti-anginal therapy.
- Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery.

*Grading of Angina Pectoris According to Canadian Cardiovascular Society Classification

Class	Description of Stage
Class I	"Ordinary physical activity does not cause . . . angina," such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation
Class II	"Slight limitation of ordinary activity." Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and under normal conditions.
Class III	"Marked limitations of ordinary physical activity." Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.
Class IV	"Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest."

15.7 Definition of Heart Failure requiring Hospitalization

Heart failure requiring hospitalization is defined as an event that meets the following criteria:

Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 12 hour stay (or a date change if the time of admission/discharge is not available)

AND

Clinical manifestation of heart failure including at least one of the following: New or worsening:

dyspnea,

orthopnea,

paroxysmal nocturnal dyspnea,

edema,

pulmonary basilar crackles,

radiological evidence of worsening heart failure.

AND

Additional/increased therapy

Initiation of IV loop diuretic, inotrope or vasodilator therapy

Uptitration of IV therapy, if already on therapy

Initiation of mechanical or surgical intervention, or use of ultra-filtration, hemofiltration or dialysis that is specifically directed at the treatment of heart failure.

Biomarker results (e.g. brain natriuretic peptide) consistent with congestive heart failure will be supportive of this diagnosis.

15.8 Definition of New Onset Diabetes

The clinical definition of Type 2 diabetes consists of the following:

a. Presence of Fasting Plasma Glucose measured on two consecutive occasions $\geq$ 126 mg/dl within 6 weeks (the Event Date will be the first of these two occasions)

Or

b. Presence of HbA1c measured on two consecutive occasions $\geq$ 6.5 % within 6 weeks in a laboratory which has validated compliance of a test that conforms to the National Glycosylation Standards Program (Little et al 2010) reference measurement of HbA1c (the Event Date will be the first of these two occasions)

Or

c. The institution and use of a diabetes medication for the purpose of glucose control by the patient including all oral agents, insulin, and injectable GLP-1 analogs. (the Event Date will be the Date noted on the prescription)

d. In the event wherein a patient has one laboratory parameter which would place them in the NOD category if repeated and confirmed within 6 weeks, then has a subsequent measurement another parameter which similarly would place them in the NOD category if repeated and confirmed within 6 weeks (e.g. FPG $\geq$ 126 mg/ dl followed by HbA1c $\geq$ 6.5%, or vice versa) will be considered to have NOD (the Event Date will be the first of these 2 occasions).

15.9 Definition of Transient Ischemic Attack

A Transient Ischemic Attack is defined as change in the blood supply to a particular area of the brain, spinal cord, or retina, resulting in brief neurologic dysfunction that persists, by definition, for less than 24 hours

Symptoms and signs

New and focal neurologic sensory and/ or motor deficits, which have a rapid onset, last no more than 24 hours and resolve completely. Symptoms may be localized to brain, spinal cord, or retina, relative to the vascular supply affecting neurologic function.

Focal sensory, reflexes, and motor lesions, which are manifestations of the arterial structure from which the insufficiency arises. All new neurologic signs resolve completely within 24 hours from the time of onset.

- Hemiplegia/paresis
- Hemianaesthesia/sensory deficit
- Hemianopsia
- Neglect
- Isolated facial weakness/droop
- Ataxia/dysmetria
- Dysarthria/speech impairment
- Aphasia
- Other

Procedure

A CT , MRI, or MRA of the brain, which demonstrates no new pathology. A neurological or neurosurgical consultation may accompany the imaging study or studies, but is not required for the diagnosis of TIA.

15.10 Definition of Critical Limb Ischemia

Critical limb ischemia is a manifestation of occlusive peripheral arterial disease that describes patients with chronic occlusive disease who demonstrate ischemic rest pain or ischemic skin lesions (either ulcers or gangrene).

Symptoms

Pain at rest, claudication, recurrent skin lesions are common.

Signs

Coolness to touch and pallor of the involved extremity may be present. Diminution or absence of pulse to palpation or bedside Doppler examination. Ulcers of the skin may be present.

Procedure

CT, MRI, MRA or angiography may be performed for diagnostic purposes. Angiographic or open revascularization may be attempted to improve arterial blood flow.

15.11 Definition of Limb Amputation due to Vascular Cause

Therapeutic resection of a limb or a portion of a limb due to a combination of vascular insufficiency, osteomyelitis, cellulitis / gangrene, or poor wound healing.

Symptoms

Symptoms may include claudication, rest pain, fever, recurrent infections. There may be a history of previous partial or complete amputations.

Signs

Decreased arterial pulse, abnormal temperature, deformity, chronic skin ulceration

Procedure

Therapeutic resection of the pathologic extremity. Reasons for amputation:

- Vascular insufficiency
- Osteomyelitis
- Cellulitis
- Gangrene
- Poor healing post-surgical wound
- Poor healing post trauma

15.12 Definition of Non-coronary Revascularization

Non-coronary revascularization is defined as vascular surgery or percutaneous intervention. Vascular surgery is defined as the placement of a conduit with or without proximal and/or distal anastamoses. Percutaneous intervention is defined as balloon inflation with or without stenting.

Symptoms

Symptoms will be specific to the arterial vasculature involved and the time of course of development of the occlusion(s).

Signs

Signs will be specific to the arterial vasculature involved and the time of course of development of the occlusion(s).

Procedures

Diagnostic CT, MRI, MRA, or Doppler US may be performed.

Revascularization or attempted revascularization with or without stenting including carotid surgery, peripheral vascular surgery or PCI, including abdominal aortic aneurysm repair, carotid revascularization, femoral, popliteal iliac, renal, open or percutaneous peripheral interventions depending on the site definition of Supraventricular Tachycardia / Atrial Fibrillation

Supraventricular tachycardia includes abnormal sinus tachycardia, ectopic atrial tachycardia atrial fibrillation/atrial flutter (with rapid ventricular response) and junctional tachycardia.

15.13 Definition of DVT

Deep vein thrombosis is defined as the pathologic presence of thrombus with inflammation, which affects the leg veins (such as the femoral vein or the popliteal vein), the deep veins of the pelvis, or rarely an upper extremity vein.

Symptoms

There may be no symptoms referable to the location of the DVT, but the classical symptoms of DVT include pain, swelling and redness of the leg and dilation of the surface veins

Signs

DVT include pain, swelling and redness of the leg and dilation of the surface veins may be present. Homan's sign, posterior calf pain on foot dorsiflexion may be present but is an insensitive indicator. Commonly, no signs are present.

Procedure

Duplex Ultrasonography is the most commonly used diagnostic test. Other tests may include d-dimer blood testing, CT with contrast, and infrequently venography. Confirmation by diagnostic study required.

15.14 Definition of PE

A Pulmonary Embolism is defined as an acute blockage of one or more pulmonary arteries by an embolus, which has originated elsewhere (usually venous thrombus) and traveled through the venous system to reach the pulmonary arteries.

Symptoms

Symptoms may include sudden-onset dyspnea, tachypnea), chest pleuritic chest pain, cough, and hemoptysis.

Signs

In addition, severe cases can include signs such as cyanosis, tachycardia, hypotension, and syncope.

Procedure

Chest X-Rays may be performed but are rarely diagnostic. Blood testing for d-dimer is often used to screen prior to performing medical imaging. Spiral CT of the chest is often performed. If significant pathology makes spiral CT less useful, a ventilation perfusion scan of the chest may be available. Confirmation by diagnostic study and localization (left or right lung and lobe) required.

15.15 Definition of Coronary Angiography

Coronary angiography is an invasive procedure wherein radiocontrast dye is introduced via an arterial catheter into the aorta, left ventricle, and coronary arteries to examine the functional capacity and anatomy of these entities.

Procedure

A radiocontrast dye is administered as described above by a cardiologist or invasive radiologist, using peripheral access into an artery (femoral or brachial).

15.16 Definition of Coronary Revascularization

Coronary revascularization is an invasive procedure, which usually follows coronary angiography, wherein either Percutaneous Transluminal Intervention, followed by Stent Placement, Balloon Angioplasty, or CABG is performed to relieve obstructed coronary arteries.

Procedure

A team of medical professionals lead by either an invasive cardiologist (Percutaneous Transluminal Intervention, followed by Stent Placement, Balloon Angioplasty,) or a thoracic surgeon (CABG), who performs the described procedures.

15.17 Definition of SVT / Atrial Fibrillation

Supraventricular tachycardia includes abnormal sinus tachycardia, ectopic atrial tachycardia atrial fibrillation/atrial flutter (with rapid ventricular response) and junctional tachycardia.

Symptoms

Symptoms may include palpitations, dyspnea, chest pain, dizziness, numbness or loss of consciousness.

Signs

Rapid heart rate, which may be regular or irregular. Peripheral pulses may be diminished or absent.

Procedure

ECG demonstrates narrow complex tachycardia originating from a site (or sites) above the ventricles. P waves may or may not be present, depending on the specific type of SVT.