NOVARTIS

Clinical Development

ACZ885M/Canakinumab

Clinical Trial Protocol CACZ885M2301 / NCT01327846

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

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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
CVD	Cardiovascular Disease
DAR	Dose Administration Record
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
eCRF	electronic Case Report/Record Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EOS	End of Study
[redacted]	[redacted]
FAS	Full Analysis Set
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GWA	Genome-wide association
HbA1c	Glycosylated hemoglobin
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus

[redacted]

hsCRP	High Sensitivity C-Reactive Protein
IA	Interim Analysis
IAC	Infection Adjudication Committee
IB	Investigators Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
[redacted]	[redacted]
IL-1β	Interleukin 1 Beta
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
i.v.	intravenous
IVRS/IWRS	Interactive Voice Response System/ Interactive Web Response System
LDL	Low density lipoprotein
LFT	Liver Function Test
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical dictionary for regulatory activities
[redacted]	
MI	Myocardial Infarction
MRS	Modified Rankin Scale
NOD	New Onset Diabetes
NYHA	New York Heart Association
OC/RDC	Oracle Clinical/Remote Data Capture
PCI	Percutaneous coronary intervention
PCP	Primary Care Physician
[redacted]	[redacted]
[redacted]	[redacted]
PP	Per Protocol Set
PPD	Purified protein derivative
PRO	Patient Reported Outcomes
PTCA	Percutaneous transluminal coronary angioplasty

[redacted]

PVD	Peripheral Vascular Disease
QFT-g	QuantiFERON-TB Gold
QoL	Quality of Life
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SBP	Systolic Blood Pressure
s.c.	Subcutaneous
[redacted]	[redacted]
SOC	System Organ Class
[redacted]	[redacted]
SMQ	Standardized MedDRA Queries
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 Diabetes Mellitus
TB	Tuberculosis
TIA	Transient Ischemic Attack
VLDL	Very-Low-Density Lipoprotein

[redacted]

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)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
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
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

[redacted]

Amendment 9

Amendment Rationale

CACZ885M2301 Protocol Amendment 9 provides details for the study extension described in the current protocol. Following accrual of the target number of primary events, eligible patients will have the option to continue study participation in the extension phase at their end of study visit. The objective of the extension phase is to obtain further follow-up information on long-term safety on continued exposure to canakinumab in trial participants. Additionally, as defined in the current protocol, [redacted]. Persistence of a potential effect of canakinumab on quality of life and the impact of a treatment switch to the open-label dose on quality of life will also be explored. Patients who choose to participate will remain on their pivotal phase blinded assigned treatment arm for the first three extension phase visits, except for prediabetic patients who will undergo a 6-month study drug washout by skipping two doses of their pivotal phase blinded assigned treatment arm. After the database from the pivotal study is locked all participants will be switched to an open-label dose of 150 mg canakinumab. The 150 mg dose is predicted to have the highest likelihood of having the most favorable benefit: risk ratio based on biomarker and clinical data from phase II studies in Type 2 diabetics. The final canakinumab dose will be based on the results from the pivotal phase. The transition to an intermediate dose of 150 mg will avoid further placebo treatment until the final dose of canakinumab is implemented at the study sites. The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first. While the extension phase is then deemed complete the safety follow-up is anticipated to be continued in registries following study results and discussion with Health Authorities.

Changes to the protocol

The described changes under the amendment rationale are implemented throughout the protocol.

In addition, the following updates, clarifications and omissions are included in this protocol amendment:

- Implementation of global and local registries post approval will be subject to discussion and agreement with health authorities during Biologic License Application (BLA)/Marketing Authorization Application (MAA) review and will be conducted via separate protocols. Section 5.5.10 updated to reflect this.

[redacted]

- Section 7.1: described the reporting of adverse events during the extension phase. During the extension phase, endpoints will no longer be collected. [redacted]
  During the extension phase ALL adverse events will be reported as AEs following the procedures described in Section 7.1 and Section 7.2.
- Section 7.2: clarification regarding the instructions for Serious Adverse Event (SAE) reporting, allowing also electronic SAE reporting
- Section 7.3 added to describe reporting of study treatment errors including misuse/abuse during the extension phase of the study
- Section 7.6.2 added that the Infections Adjudication Committee will not adjudicate cases during the extension phase
- Section 7.6.3 added that the Malignancy Adjudication Committee will not adjudicate cases during the extension phase
- Section 10.5 added to describe the Quality Management system that applies to this trial.

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, sites are required to submit for approval an updated informed consent that covers the extension phase of the study, which will be signed by patients before they move into main drug dispensing period (Visit 201 and beyond) of the extension phase.

Other minor updates and corrections were also included.

Summary of previous amendments

Amendment 8

Amendment Rationale

CACZ885M2301 Protocol Amendment 8 adjusts the number of patients to be randomized into the study from 17,200 patients to approximately 10,000 patients. This change is not based on safety or efficacy concerns, instead it resulted from a strategic decision that considered the higher than anticipated primary event endpoint rate observed thus far.

Importantly, the study objectives and power remain unchanged and the study will still complete when 1,400 primary event endpoints are accrued as originally planned. The elapsed calendar time to reach the conclusion of the study is now estimated to be approximately 6 years (instead of 5 years) of treatment and follow-up from the start of enrollment in the trial to when 1,400 primary cardiovascular events have been accrued.

[redacted]

Protocol Amendment 8 also introduces the option to perform a futility analysis earlier than the first planned efficacy interim analysis (IA) (at approximately 50% primary events) but only after a sufficient number of primary events are accrued, i.e., >25%. This may be performed by the DMC in consideration of the longer period of time that may be needed to reach the first IA from the start of enrollment.

Changes to the protocol

The described changes in the amendment rationale are implemented throughout the protocol.

The following minor updates, clarifications and omissions are included in this protocol amendment:

- In accordance with the change in sample size, the total planned patients screened changed from 29,000 to 17,000.
- Spelled out the CANTOS acronym (Section 3.1)
- Informed that CACZ885M2301 Sub-study S1 and S2 have been terminated. Of note, the Sponsor decision to terminate these sub-studies was not due to safety or efficacy concerns (Section 3.1).
- Clarified that the full committee DMC safety reviews will occur on a six-month basis and the DMC chair will review the safety data on a three-month basis (Section 3.5).
- In Section 5.5.8, added information specifying that the patient contact information should be reviewed at each visit and clarified the process for visits/patient contact following study drug discontinuation.
- Added Years 5 and 6 to Table 6-1
- In Section 6.5.7, informed as a correction that Allergies/Immunological are not adjudicated events.
- Corrected the following statement noting that all malignancies including basal cell carcinoma should be reported as SAEs meeting the criteria of "medically significant" (Section 7.1)
- In the site monitoring section (Section 8.1), incorporated the various methods utilized to ensure protocol and GCP compliance and the quality/integrity of the sites' data. Continuous remote monitoring and a central analytics organization have been added as a complement to field monitoring.
- A discussion of the currently observed event rates, the impact on trial duration and the lack of an impact on study power was added to the statistical section.

Other minor updates and corrections were also included.

Amendment 7

Short summary of the amendment rationale and major changes

[redacted] Visit 1 screening tests for HBc antibody and HBs antibody are added in Japan only to prevent enrolling Japanese patients who have a history of hepatitis B infection and/or are hepatitis B carriers. In

[redacted]

[redacted] specific language regarding post-menopausal status determination in women less than 50 years of age is added for Croatia only.

Additional updates and clarifications were also noted in this protocol amendment such as allowing the prescreen hsCRP if performed at the central laboratory less than 60 days prior to Visit 2 and ≥ 2mg/L to be used as the qualifying hsCRP, clarifying the tuberculosis status determination for study entry, informing that recruitment will target approximately 50% of randomized patients with an index MI 30 days to 12 months prior to randomization and 50% with an index MI >12 months prior to randomization, and noting that for patients whose treatment is stopped as a result of a data monitoring committee recommendation to suspend treatment in one dose group, follow-up for cardiovascular and safety events will continue at 6 month intervals. The amendment also removed mention of a recruitment duration of 21 months and informed that the elapsed calendar to time to reach the conclusion of the study is estimated to be approximately 5 years of treatment from the start of enrollment to the occurrence of when 1,400 patients have had confirmed adjudicated primary cardiovascular events. In Section 5.5.8, additional clarity was added to the situations under which patients may restart study treatment, the liver function test discontinuation criteria was aligned with recent company guidance for liver enzyme elevations, and it was noted that patients who develop any malignancy other than excised basal cell skin carcinoma must discontinue from study treatment. [redacted]

Other minor updates and corrections were also included.

Amendment 6

Short summary of the amendment rationale and major changes

[redacted] Amendment 6 included a lower 50 mg dose arm in order to examine canakinumab's dose response in preventing recurrent cardiovascular events, [redacted]

Amendment 6 also increased the sample size to 17,200 patients in order to have the power of having at least one dose significant of ≥ 90% and to also have ≥ 80% power for the 50 and 150 mg doses individually when assuming that all doses have a 20% relative risk reduction. Following this amendment, randomized allocation to the four trial arms will be unbalanced in order to optimize power, now that three active arms are compared versus a common control arm. Overall across both trial parts an approximately 1.5:1:1:1 (placebo: 50 mg canakinumab: 150 mg canakinumab: 300 mg canakinumab) allocation is targeted.

[redacted]

Amendment 6 also clarified the documentation requirements for spontaneous MI inclusion criteria, women of child-bearing potential exclusion criteria and tuberculosis exclusion criteria. [redacted] The analysis plan was updated to insert the evaluation of the 50 mg dose into the pre-specified closed testing procedure for primary and key secondary endpoints.

Amendment 5

Short summary of the amendment rationale and major changes

In order to comply with the European Competent Authorities request in the context of the Voluntary Harmonization Procedure (VHP), additional information regarding potential early study termination was added to Section 5.5.1.

Amendment 4

Short summary of the amendment rationale and major changes

[redacted] additional instruction for reporting of specific pre-defined endpoints in Japan was added. This instruction applies to Japan only. Section 7.2 describes the specific pre-defined endpoints in Japan that require expedited reporting to Novartis Pharma K.K.

Amendment 3

Short summary of the amendment rationale and major changes

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.

[redacted]

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 (5.6-6.9 mmol/L), 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;

[redacted]

(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:

- [redacted]
- Troponin I and creatinine kinase MB fraction were added for patients with elevated total creatinine kinase
- [redacted]
- SAE reporting instructions were corrected to direct investigators to follow instructions provided in the investigator folder
- [redacted]
- [redacted]
- Diabetes related definitions used in stratification section were updated
- [redacted]
- HOMA calculation was removed
- A confirmation of elevated ALT/AST and total bilirubin is no longer required at screening

[redacted]

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 prediabetes, will prevent new onset diabetes (NOD) will also be tested. [redacted] An optional extension to the study will be conducted following the completion of the pivotal phase with the purpose to further characterize long-term safety on continued exposure to canakinumab in trial participants.

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 (standard of care)-controlled setting
- Extension: to obtain further follow-up information on long-term safety on continued exposure to canakinumab in trial participants

[redacted]

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 ≥ 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 pivotal phase will be an event-driven global trial conducted in the outpatient setting. It is anticipated that approximately 1,400 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 approximately 17,000 patients will need to be screened in order to randomize approximately 10,000 patients. All participants of the pivotal phase who continue to be eligible to receive study drug will be offered the option to enter the extension phase.

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 ≥ 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 the qualifying 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. For details, refer to the Universal Definition of MI (Thygesen et al 2007).
   - Please see below for documentation requirements.
     a. Acute MI (hospitalization records): requires documentation of a rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th

percentile of the upper reference limit (URL) or above criteria diagnostic for MI AND evidence of myocardial ischemia as demonstrated by at least one of the following :

i. Symptoms of ischemia
ii. ECG changes indicative of new ischemia (new ST-T changes or new LBBB)
iii. Development of pathologic Q waves (please see appendix 3 for definitions of pathological Q waves)
iv. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

b. Prior MI (no hospital records for acute event available): requires documentation of any one of the following :

i. Development of pathological Q waves with or without symptoms (please see appendix 3 for definitions of pathological Q waves)
ii. 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
iii. Pathologic findings of a healed or healing MI

- Patients with MI resulting from PCI or CABG will not be eligible

5. Have an hsCRP ≥ 2 mg/L at screening (Visit 1) (collected less than 60 days prior to Visit 2 and performed at the central laboratory, which is a minimum of 28 days after qualifying MI or after any PCI performed separately from qualifying MI) on stable (at least 4 weeks) long-term (cardiovascular) 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
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 have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone or partial or total hysterectomy, 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

     [For Croatia only]

     [In Croatia, women who are < 50 years of age must have >2 years of amenorrhea or minimum of 1 year of amenorrhea with FSH levels of ≥40 IU determined on 2 or more occasions at least one month apart]
3. Any of the following concomitant diseases
   - Planned coronary revascularization (PCI or CABG) or any other major surgical procedure
   - Major non-cardiac surgical or major endoscopic procedure within the past 6 months prior 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).

[redacted]

- 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), at Visit 1
- Known active or recurrent hepatic disorder (including cirrhosis, hepatitis B and hepatitis C (positive or indeterminate central laboratory results), 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 tuberculosis (TB) (active or latent) infection or one of the risk factors for TB 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
   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.
   c. Evidence of TB (active or latent) infection, at Visit 1, determined by purified protein derivative (PPD) skin test and/or QuantiFERON®-TB Gold (QFT-g) assay as defined by country guidelines.
      i. If presence of TB (active or latent) is established, then treatment (according to country guidelines for TB treatment or TB treatment with immunomodulating drugs) must have been initiated or completed prior to randomization per country guidelines.
      ii. In the absence of country TB (active or latent) guidelines, the following has been demonstrated: TB has been treated adequately with antibiotics, cure can be demonstrated, and risk factors resulting in TB exposure and contracting TB have been removed (e.g. the patient does not live anymore in high TB exposure setting).
6. History of ongoing, chronic or recurrent infectious disease
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 or intravenous steroids (> 20 mg prednisone orally daily for > 14 days, > 5 mg prednisone orally daily or equivalent dose of intravenous steroid) or high dose methotrexate (> 15 mg weekly). 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 drug 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 than vascular disease that might prevent the patient from completing the study

Investigational and reference therapy:

[redacted]

Following protocol amendment 6 (trial part 2) patients will be assigned to one of the following 4 treatment arms in a ratio of 1.3 : 1.3 : 1.4 : 2

- 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
- 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 50 mg s.c. at randomization, placebo s.c. at week 2, 50 mg s.c. at week 12, and thereafter 50 mg s.c. quarterly
- Placebo s.c. at randomization, at week 2, at week 12, and thereafter quarterly

Prior to protocol amendment 6 (trial part 1) patients were 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

Across trial parts 1 and 2 this is expected to approximately result in a 1:1:1:1.5 allocation.

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 restart medication at any time during the study at the discretion of the investigator.

For the extension phase, all participants except for prediabetic patients will remain on their pivotal phase assigned treatment arm for the first three extension phase visits (Month 0 to Month 6). After the database from the pivotal study is locked they will be switched to an open-label dose of 150 mg canakinumab at the fourth scheduled extension visit (visit Month 9) (Figure 3-2). The 150 mg dose will be administered until the final dose of canakinumab is implemented at the study sites based on the results from the pivotal phase. In contrast to all other participants of the pivotal phase, patients with both randomization and pivotal phase EOS prediabetes will enter a 6-month study drug washout at the beginning of the extension phase by skipping two doses of their pivotal phase blinded assigned treatment arm. At their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) they will receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3).

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. The study is composed of a pivotal phase and an extension phase. The pivotal phase is composed of the screening period and the double blind treatment period. The extension phase is composed of the study drug washout period in prediabetic patients and the main drug dispensing period. PreScreening/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.

[redacted]

Randomization will be stratified by time since most recent index myocardial infarction (30 days to <6 months and ≥6 months). Recruitment will target approximately 50% of randomized patients with index MI 30 days to 12 months prior to randomization and 50% of randomized patients with index MI > 12 months prior to 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. The trial is event driven and designed to complete when a total of 1,400 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 a pivotal phase EOS visit. The elapsed calendar time to reach conclusion of the study is estimated to be approximately 6 years of treatment and follow-up from the start of enrollment in the trial to the occurrence of 1,400 confirmed adjudicated cardiovascular events.

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. A futility analysis may be performed earlier than the first planned efficacy IA (at approximately 50% primary events) but only after a sufficient number of primary events are accrued, i.e., >25%.

Following the completion of the pivotal phase, every patient who continues to be eligible to receive study drug will be offered the option to continue study drug treatment during the extension phase. The objective of the extension phase is to further characterize long-term safety on continued exposure to canakinumab in trial participants. Consenting patients will be scheduled for visits to dispense study drug and to collect safety data at 3-month intervals. All participants except for prediabetic patients will remain on their pivotal phase assigned treatment arm for the first three extension phase visits (Month 0 to Month 6). After the database from the pivotal study is locked they will be switched to an open-label dose of 150 mg canakinumab at the fourth scheduled extension visit (visit Month 9) (Figure 3-2). The final canakinumab dose will be based on the results from the pivotal phase. The transition to an intermediate dose of 150 mg will avoid further placebo treatment until the final dose of canakinumab is implemented at the study sites. In contrast to all other participants of the pivotal phase, patients with both randomization and pivotal phase EOS prediabetes will enter a 6-month study drug washout at the beginning of the extension phase by skipping two doses of their pivotal phase blinded assigned treatment arm. At their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) they will receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3).

[redacted] The extension phase will collect all safety events (serious and non-serious AEs) including malignancies, infections and major cardiovascular adverse events that were defined as the primary endpoint of the pivotal phase. No adjudication of events will be performed, neither for CV events nor serious infections or malignancies during the extension phase. The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first. While the extension phase is then deemed complete the safety follow-up is anticipated to be continued in registries following study results and discussion with Health Authorities.

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, [redacted]

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

[redacted]

Safety Assessments*:*

- Laboratory evaluations
- Height, weight and waist circumference
- Adverse events and serious adverse events, including cardiovascular events, malignancies, and infections
- Discontinuation due to AEs
- Hypoglycemia events
- Injection site reactions
- Physical Examination
- [redacted]
- 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.

The extension phase will collect all safety events (serious and non-serious AEs) including malignancies, infections and major cardiovascular adverse events that were defined as the primary endpoint of the pivotal phase. No adjudication of events will be performed, neither for CV events nor serious infections or malignancies.

[redacted]

Data analysis:

[redacted]

The primary statistical hypotheses are:

- H_{11}: 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
- H_{21}: 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_{31}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 50 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 and by trial part using exact method 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 to the primary null hypotheses relating to the three 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. This constitutes an equivalent level of evidence as the two-sided 5% level and two-sided p-values will also be reported.

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) and by trial part using treatment (canakinumab doses and placebo) as a factor in the model using exact method for handling ties. Kaplan-Meier type plots will be presented overall and separately by trial part 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 by trial part, and displayed by means of Kaplan-Meier type plots according to treatment overall and by trial part.

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 (≥ 7.0 mmol/L) or of a repeated HbA1c $\geq$ 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 exact method for handling ties will be used.

[redacted]

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.

[redacted]

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.

From the extension phase, the incidence of adverse events (new or worsening) will be summarized by primary system organ class (SOC), preferred term, severity and relationship to study drug. SAEs and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term. The incidence of death will be summarized by the primary cause.

Sample Size Calculation

With a sample size of approximately 10,000 randomized patients and assigned in a 1:1:1 allocation ratio to canakinumab 150 mg, canakinumab 300 mg, and placebo in trial part 1 and in a 2 : 1.4 : 1.3 : 1.3 allocation ratio to placebo, canakinumab 50 mg, canakinumab 150 mg, and canakinumab 300 mg in trial part 2, it is expected that 1,400 patients will experience a primary endpoint approximately 6 years after study initiation. 1,400 endpoints are necessary to achieve a power ≥ 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 20% for all active doses and to also have ≥ 80% power for the 50 and 150 mg doses individually.

No sample size calculation was performed for the extension phase, because the key objective of the extension phase is long-term safety assessment in participants of the pivotal phase.

[redacted]

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). [redacted]

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 [redacted]

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 glycosylated hemoglobin (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

[redacted]

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 prediabetes, will prevent new onset diabetes (NOD) will also be tested. [redacted]

The purpose of the extension phase is to collect additional long-term safety data on continued exposure to canakinumab in patients who participated in the pivotal phase.

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.

[redacted]

- To demonstrate superiority of canakinumab as compared to placebo on the endpoint of all-cause mortality

Safety objectives

- To evaluate the long-term safety of canakinumab therapy in a placebo(standard of care) - controlled setting
- Extension phase: to obtain further follow-up information on long-term safety on continued exposure to canakinumab in trial participants

[redacted]

[redacted]

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 CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) study is designed to evaluate the benefit of quarterly doses of 50 mg and 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 (Note: centrally-performed prescreen hsCRP results must be obtained less than 60 calendar days prior to Visit 2 to be used to evaluate Inclusion criterion 5, Section 4.1).

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.

The Pre-screening visit 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. Pre-screening can only be initiated following this procedure.
- 3 years post a Multi-vessel CABG procedure regardless of timing of the qualifying MI

Patients with a prescreen hsCRP ≥ 2 mg/L from the central laboratory do not require an hsCRP measurement at Visit 1, provided the prescreen hsCRP blood sample was drawn less than 60 days prior to Visit 2 and the patient is on stable (at least 4 weeks) long term medications. All pre-screened patients must be called into the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). Note: The Pre-screening visit should not occur and instead be rescheduled if the patient presents with an acute viral or bacterial infection at the Pre-screen visit.

Screening: Screening will take place no earlier than:

[redacted]

- 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 Multi-vessel CABG procedure regardless of timing of the qualifying MI.

All screened patients must be called into the IVRS/IWRS. Screening evaluations will include determination of tuberculosis status, other measurements and procedures, and hsCRP measurement in patients who proceeded directly to Visit 1 due to a prior (non-centrally performed) hsCRP, ≥ 2mg/L performed 60 days to prior Visit 1. After the screening visit, patients may be randomized as soon as results from the screening laboratory and other studies are available. However, this can be no earlier than 30 days after the index MI. Note: For patients who require an hsCRP measurement at Visit 1 only, the Screening Visit/Visit 1 should not occur and instead be rescheduled if the patient presents with an acute viral or bacterial infection at Visit 1.

The time between screening and randomization should be approximately 4 weeks with the qualifying centrally-performed hsCRP obtained no less than 60 days prior to Visit 2 (Note: the maximum amount of time between Visit 1 and Visit 2 should not exceed 60 days with the exception of those who initiate treatment for tuberculosis (TB) as described below). 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 (applicable for out of range systolic and diastolic blood pressure and patients requiring TB treatment. Note: Patients who initiate treatment for TB and who per country guidelines can be randomized into the trial < 60 days after starting TB treatment, must have a repeat hsCRP performed just prior to randomization which is ≥ 2 mg/L; those who can be randomized into the trial > 60 days after starting TB treatment, must be re-evaluated just prior to randomization for all Inclusion/Exclusion criteria including central laboratory evaluations). Patients re-evaluated will retain their screening number and be randomized or screen failed based upon the result of the re-evaluation.

Randomization: Randomization will be stratified by time since most recent index myocardial infarction (30 days to <6 months and ≥6 months). Recruitment will target approximately 50% of randomized patients with index MI 30 days to 12 months prior to randomization and 50% of randomized patients with index MI > 12 months prior to randomization. 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, [redacted] 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/

[redacted]

or placebo. [redacted]

The pivotal phase is event driven and designed to complete when a total of 1,400 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 pivotal phase EOS visit. The elapsed calendar time to reach conclusion of the study is estimated to be approximately 6 years of treatment and follow-up from the start of enrollment in the trial to when 1,400 patients have had a confirmed adjudicated cardiovascular event.

Extension phase: At the first visit of the extension phase (visit Month 0), every trial participant who continues to be eligible to receive study drug will be offered the option to continue study drug treatment during the extension phase. Consenting patients will remain at the 3-month intervals between study visits as shown in the study assessment schedule for the extension phase (Table 6-2 and Table 6-3). All patients must be called into the IVRS/IWRS at every visit throughout the extension phase. For all participants except for prediabetic patients the first visit of the extension phase at Month 0 should occur on the same day as the pivotal phase EOS visit. In case the last drug administration of the pivotal phase occurred within 4 weeks before the pivotal phase EOS visit, the study drug administration at the extension phase Month 0 visit will be skipped and the first injection as part of the extension phase will be performed at the Month 3 visit. All participants except for those with prediabetes will remain on their pivotal phase assigned treatment arm for the first three extension phase visits (Month 0 to Month 6). After the database from the pivotal study is locked they will be switched to an open-label dose of 150 mg canakinumab at the fourth extension phase visit (Month 9) (Figure 3-2). The 150 mg dose is predicted to have the highest likelihood of having the most favorable benefit: risk ratio based on biomarker and clinical data from phase II studies in Type 2 diabetics. The final canakinumab dose will be based on the results from the pivotal phase. The transition to an intermediate dose of 150 mg will avoid further placebo treatment until the final dose of canakinumab is implemented at the study sites. In contrast to all other participants of the pivotal phase, patients with both randomization and EOS prediabetes will enter a 6-month study drug washout at the beginning of the extension phase by skipping two doses of their pivotal phase blinded assigned treatment arm. At their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) they will receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3 (Figure 3-3). The pivotal phase EOS glycemic status will be assessed based on the last HbA1c and fasting plasma glucose (FPG) data available at the EOS visit. For participants of the prediabetes washout, the first visit of the extension at Month 0 should occur on the same day as the End of Prediabetes Washout visit. The extension phase will collect all safety events (serious and non-serious AEs) reported and will no longer adjudicate any pre-specified efficacy or safety events. In addition to safety assessments at every visit, annual vital sign measurements will be performed according to the extension phase assessment schedule. The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled

[redacted]

in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first. Once study closeout date is determined, the site staff is contacted to have the patients return for their extension phase EOS visit. While the extension phase is then deemed complete the safety follow-up is anticipated to be continued in registries following study results and discussion with Health Authorities.

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 per study schedule (i.e., every 3 months) 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.

For patients whose treatment is stopped as a result of a Data Monitoring Committee (DMC) recommendation to suspend treatment in one dose group, follow-up for cardiovascular (CV) and safety events will continue. Since these patients will not receive further study medication, less frequent follow-up will be conducted every 6 months. Continued follow-up will likely enhance understanding of the safety of the other dose groups.

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

Extension phase: for patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

End of Study Follow-up for all prediabetic patients

Once all study endpoints of the pivotal phase have been reached and the site staff is contacted to have all patients return for their pivotal phase EOS visit, any patient with a prediabetic status at both randomization and at pivotal phase EOS visit (based on last lab results available at the EOS visit), will enter into an additional 6-month washout without study drug treatment by skipping two doses of their pivotal phase blinded assigned treatment arm. At the end of the study drug washout, HbA1c and FPG will be performed along with the other study procedures shown in Table 6-3. If no HbA1c value is available from the End of Prediabetes Washout visit or if a diabetes diagnosis is only based on one FPG value of ≥ 126 mg/dL (≥ 7 mmol/L) from the End of Prediabetes Washout visit, an unscheduled visit should be conducted within 6 weeks. The purpose of this washout period is to assess to what extent a potential lower incidence of diabetes diagnoses observed on canakinumab relative to placebo during pivotal phase 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

[redacted]

washout. At their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) study drug washout participants will receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3).

No adjudication of NOD will be performed during the extension phase.

Sub-Studies

All patients who suffer a stroke during the double-blind period of the pivotal phase will participate in the, Post-Stroke Functional Assessment Sub-Study; see Section 6.6.5 for further details.

The CACZ885M2301S1 imaging sub-study (to evaluate the effect of quarterly subcutaneous canakinumab treatment for 24 months versus placebo, on top of standard of care, on the carotid plaque burden measured by vascular MRI in approximately 330 patients) and the CACZ885M2301S2 oral glucose tolerance test sub-study (to determine whether canakinumab compared to placebo, on top of standard of care, increases insulin secretion and insulin sensitivity in approximately 300 patients with type 2 diabetes) were prematurely terminated. The termination was not due to safety or efficacy concerns.

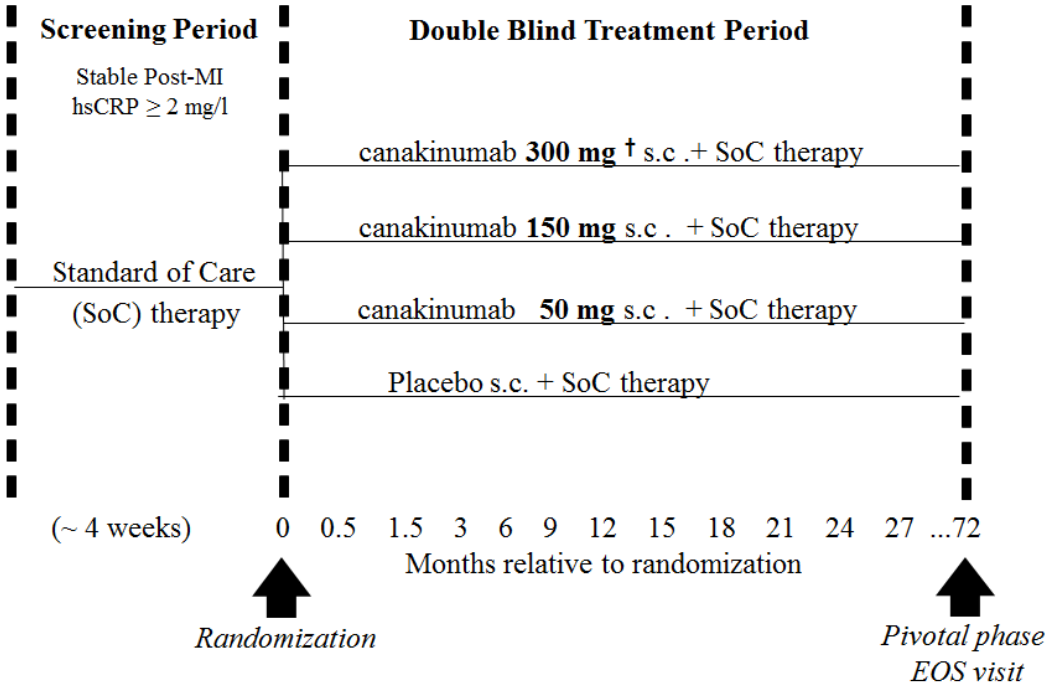
Interim Analysis

Interim analyses will be conducted for this trial; please see Section 3.5 and Section 9.8 for details.

[redacted]

Figure 3-1 Study design pivotal phase

The pivotal phase is composed of the screening period and the double blind treatment period.

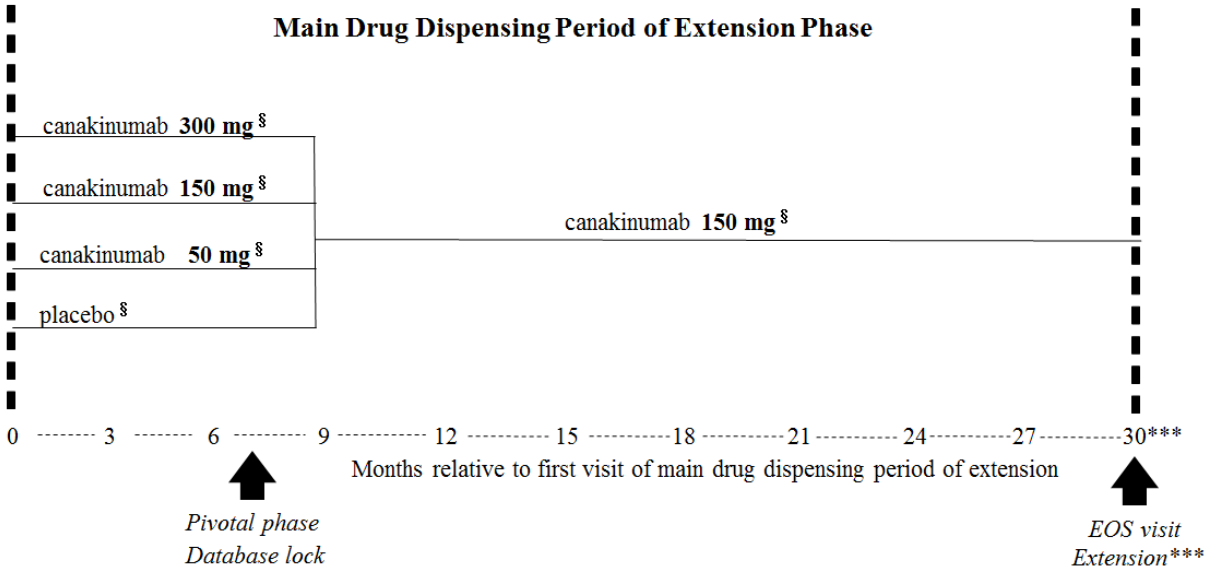


†- canakinumab 300 mg s.c. induction at randomization (month 0) and week 2 (month 0.5), and then 300 mg s.c. quarterly beginning at week 12.

Figure 3-2 Study design of extension phase for patients <u>not</u> participating in study drug washout

For patients not participating in the 6-month study drug washout period, the extension phase is only composed of the main drug dispensing period.

[redacted]



§plus Standard of Care therapy

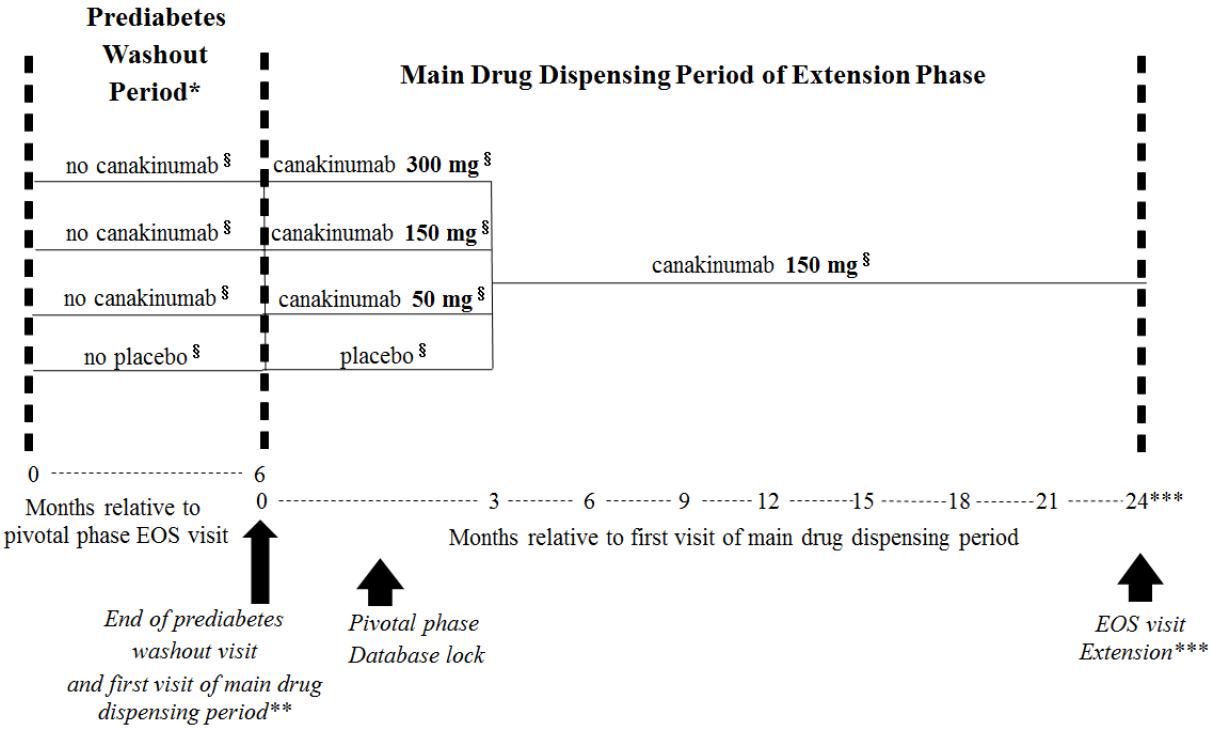
***The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first.

Patients who choose to participate in the extension phase will remain on their pivotal phase blinded assigned treatment arm for the first three extension phase visits (Month 0 to Month 6). After the database from the pivotal study is locked they will be switched to an open-label dose of 150 mg canakinumab at the fourth extension visit (Month 9). The final canakinumab dose will be based on the results from the pivotal phase. The transition to an intermediate dose of 150 mg will avoid further placebo treatment until the final dose of canakinumab is implemented at the study sites.

Figure 3-3 Study design of extension phase for prediabetic patients

For patients with prediabetic status at both randomization and pivotal phase EOS visit the extension phase is composed of the study drug washout period and the main drug dispensing period.

[redacted]



§plus Standard of Care therapy

*Only patients with prediabetic status from both randomization and pivotal phase EOS visit will enter the study drug washout.

**After the End of Prediabetes Washout visit, the patients will enter the subsequent main drug dispensing period of the extension. The first visit of the main drug dispensing period should occur on the same day as the End of Prediabetes Washout visit.

***The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first.

Prediabetic patients will participate in a 6-month study drug washout at the beginning of the extension phase by skipping two doses of their pivotal phase blinded assigned treatment arm. At their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) study drug washout participants will receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3, as shown in Figure 3-3).

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.

[redacted]

The design of the extension phase is appropriate to enable the collection of additional long-term safety data for the investigational drug and to provide patients the opportunity to receive treatment with canakinumab until marketed product is available. The study design also allows to evaluate changes in glycemic status following study drug washout in patients with prediabetes in order to assess the durability of any potential antidiabetic effect after study drug discontinuation. Enrollment will be available to all patients who participated in the pivotal phase and who continue to be eligible to receive study drug.

3.3 Rationale of dose/regimen, duration of treatment

Canakinumab 50 mg and 150 mg quarterly

The 50 mg and 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. 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, 50 mg monthly as fully efficacious dose and 15 mg monthly as submaximal dose were selected for further development. 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 and 50 mg quarterly dosing had similar free IL-1β suppression compared to 15 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. Therefore, canakinumab 50 mg and 150 mg quarterly administration were selected for the doses in this study, CACZ885M2301. The selected doses allow examination canakinumab dose response in preventing recurrent cardiovascular events and to determine if a lower dose than 150 mg would have a favorable risk benefit ratio.

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

[redacted]

positive feedback mechanism for vascular disease including atherosclerosis. The lower 50 mg and 150 mg quarterly doses does not include an early high, induction dose regimen to ensure separation of the three 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.

Induction dose in the 300 mg quarterly dose arm

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.

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.

[redacted]

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 50 mg s.c. at randomization (month 0), placebo s.c. at week 2 (month 0.5), canakinumab 50 mg s.c. at week 12 (month 3), and then canakinumab 50 mg s.c. quarterly; (c) 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 (d) 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.

Dosing regimen in extension phase

Every trial participant who continues to be eligible to receive study drug will be offered the option to continue study drug treatment during the extension phase. Consenting patients except those with prediabetes will remain on their pivotal phase assigned treatment arm for the first three extension phase visits (Month 0 to Month 6). After the database from the pivotal phase is locked, participants will be switched to an open-label dose of 150 mg canakinumab at the fourth scheduled extension visit (visit Month 9) (Figure 3-2). The 150 mg dose is predicted to have the highest likelihood of having the most favorable benefit: risk ratio based on biomarker and clinical data from phase II studies in Type 2 diabetics. The final canakinumab dose will be based on the results from the pivotal phase. The transition to an intermediate dose of 150 mg will avoid further placebo treatment until the final dose of canakinumab is implemented at the study sites. The first drug administration as part of the extension will be performed at the first visit of the main drug dispensing period of the extension phase. The first visit of the main drug dispensing period at Month 0 should occur on the same day as the pivotal phase EOS visit. In case the last drug administration of the pivotal phase occurred within 4 weeks before the pivotal phase EOS visit, the study drug administration at the extension phase Month 0 visit will be skipped and the first injection as part of the extension phase will be performed at the Month 3 visit. In contrast to all other participants of the pivotal phase, prediabetic patients will enter a 6-month study drug washout at the beginning of the extension phase after which they will restart study drug administration as part of the extension phase. For participants of the prediabetes washout, the first visit of the subsequent main drug dispensing period of the extension at Month 0 should occur on the same day as the End of Prediabetes Washout visit. At this Month 0 visit study drug washout participants will receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3).

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

[redacted]

was felt that it would be unethical to restrict use of proven benefit high dose statin therapy to the comparator arm only. No active comparator will be used in the extension phase. Additionally, no placebo drug will be used from extension visit Month 3 onwards (participants of study drug washout period) and from Month 9 onwards (all other participants of extension phase).

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, and one additional futility analysis may also be performed earlier than the first planned efficacy IA (at approximately 50% primary events), but only after a sufficient number of primary events are accrued, i.e., >25%. 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 (full committee) and on a three-month basis (chair only).

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:

[redacted]

Definition of randomization Pre-Diabetes

- At visit 1 OR 2 HbA1c of 5.7-6.4% or FPG 100-125 mg/dL (5.6-6.9 mmol/L) (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 ≥6.5% (visit 1 and visit 2)

    or
  - FPG ≥ 126 mg/dL (≥7.0 mmol/L) (visit 1 and visit 2).

    or
  - Combination of FPG ≥ 126 mg/dL (≥7.0 mmol/L) and HbA1c ≥6.5% (visit 1 and visit 2)

Definition of Prediabetes at the End of Study Visit

- At randomization and at the EOS visit of the pivotal phase (based on the last available HbA1c and FPG measurement prior to the EOS visit) having prediabetes as defined by HbA1c of 5.7-6.4% or FPG 100-125 mg/dL (5.6-6.9 mmol/L) (ADA 2010 Clinical Practice Recommendations)

The pivotal phase will be an event-driven global trial conducted in the outpatient setting. It is anticipated that approximately 1,400 patients with adjudication committee confirmed cardiovascular endpoints will accrue during the course of the pivotal phase (see Section 9.7 for Power Calculations). To accomplish this goal, it is expected that approximately 17,000 patients will need to be screened in order to randomize approximately 10,000 patients. All participants of the pivotal phase who continue to be eligible to receive study drug will be offered the option to enter the extension phase.

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 the qualifying 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)

[redacted]

OR development of new pathological Q waves regardless of symptoms. For details, refer to the Universal Definition of MI (Thygesen et al 2007).

- Please see below for documentation requirements.
  a. Acute MI (hospitalization records): requires documentation of a rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) or above criteria diagnostic for MIAND evidence of myocardial ischemia as demonstrated by at least one of the following :
     i. Symptoms of ischemia
     i. ECG changes indicative of new ischemia (new ST-T changes or new LBBB)
     ii. Development of pathologic Q waves (please see appendix 3 for definitions of pathological Q waves)
     iii. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  b. Prior MI (no hospital records for acute event available): requires documentation of any one of the following :
     i. Development of pathological Q waves with or without symptoms (please see appendix 3 for definitions of pathological Q waves)
     ii. 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
     iii. Pathologic findings of a healed or healing MI
- Patients with MI resulting from PCI or CABG will not be eligible

5. Have an hsCRP ≥ 2 mg/L (collected less than 60 days prior to Visit 2 and performed at the central laboratory, which is a minimum of 28 days after qualifying MI or after any PCI performed separately from qualifying MI) on stable (at least 4 weeks) long term (cardiovascular) 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
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 have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone or partial or total hysterectomy, 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.

   [For Croatia only]

[redacted]

[In Croatia, women who are < 50 years of age must have >2 years of amenorrhea or minimum of 1 year of amenorrhea with FSH levels of ≥40 IU determined on 2 or more occasions at least one month apart]

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 major endoscopic procedure within the past 6 months prior 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).
   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 (positive or indeterminate central laboratory results), or alanine aminotransferase/ aspartate aminotransferase (ALT/AST) levels > 3 times ULN or total bilirubin > 2 times ULN) atVisit 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 tuberculosis (TB) (active or latent) infection 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
   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.
   c. Evidence of TB infection (active or latent), at Visit 1, determined by purified protein derivative (PPD) skin test and/or QuantiFERON®-TB Gold (QFT-g) assay as defined by country guidelines (refer to Determination of Tuberculosis Status, p.39).
      i. If presence of TB (active or latent) is established then treatment (according to country guidelines for TB treatment or TB treatment with immunomodulating drugs) must have been initiated or completed prior to randomization per country guidelines.

[redacted]

ii. In the absence of country TB (active or latent) guidelines, the following has been demonstrated: TB has been treated adequately with antibiotics, cure can be demonstrated, and risk factors resulting in TB exposure and contracting TB have been removed (e.g. the patient does not live anymore in high TB exposure setting).

6. History of ongoing, chronic or recurrent infectious disease
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 or intravenous steroids (> 20 mg prednisone orally daily for > 14 days, > 5 mg prednisone orally daily or equivalent dose of intravenous steroid) or high dose methotrexate (> 15 mg weekly). 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 drug 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 than vascular disease that might prevent the patient from completing the study

Determination of tuberculosis status

Determination of tuberculosis (active or latent) status, either by performing the PPD skin test or the QFT-g assay will be required before administration of study drug and should be performed as defined by country guidelines. Patients need to have given written informed consent before any of these assessments are initiated. Patients who have had a negative PPD skin test or negative QFT-g assay performed within 30 days of screening (Visit 1) will not need repeat testing performed to determine eligibility. All other patients will need tuberculosis (active or latent) 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 positive or indeterminate QFT-g test may still participate in the study if

[redacted]

1. Treatment of tuberculosis (active or latent) (according to country guidelines) has been initiated or completed prior to randomization

or

2. Patients with a history of TB who were treated must demonstrate that treatment has been received and further work up (according to country practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis.

or

3. The repeat QFT-g test is negative in patients with an indeterminate QFT-g result at Visit 1.

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. In case of a positive PPD skin test, the patient may be further screened for latent TB infection by performing the QFT-g 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 (QFT-g) assay may be performed to assess the TB (active or latent) 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 (BCG) 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.

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

Chest x-ray

A chest x-ray may be performed if required by country regulations in case of positive PPD skin test or positive QFT-g assay but will not be part of eligibility assessment.

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

[redacted]

Tuberculosis status will not be re-assessed during the extension phase.

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.

Two strengths and respective corresponding matching placebos will be supplied:

- Canakinumab 50 mg in 0.5 mL solution for injection and one placebo formulation matching to this active drug formulation.
- Canakinumab 150 mg in 1 mL solution for injection and one placebo formulation matching to this 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 for patients randomized to randomization plan A, one syringe of 1ml and one syringe of 0.5 ml for patients randomized to randomization plan B) 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. The minimum time between dosing visits after Visit 3 is 30 days.

Table 5-1 Injection Description

Randomization Plan	Treatment Groups	Injections at all visits excluding Screening, month 0.5 and 1.5 visits	Injections at Visit month 0.5
A	Canakinumab 150 mg sc	1 x canakinumab 150 mg and 1 x matching placebo	2 x placebo matching canakinumab 150 mg
A	Canakinumab 300 mg sc	2 x canakinumab 150 mg	2 x canakinumab 150 mg
A	Placebo	2 x placebo matching canakinumab 150 mg	2 x placebo matching canakinumab 150 mg
B	Canakinumab 50 mg sc	1 x canakinumab 50 mg and 1 x 150 mg matching placebo	1 x placebo matching canakinumab 50 mg 1 x placebo matching canakinumab 150 mg

[redacted]

B	**Canakinumab 150 mg sc**	**1 x canakinumab 150 mg and 1 x 50 mg matching placebo**	**1 x placebo matching canakinumab 50 mg 1 x placebo matching canakinumab 150 mg**
B	**Placebo**	**1 x 50 mg matching placebo and 1 x 150 mg matching placebo**	**1 x 50 mg matching placebo and 1 x 150 mg matching placebo**

In the extension phase, all participants except for those with prediabetes will remain on their pivotal phase randomization plan and treatment group for the first three extension phase visits (Month 0 to Month 6). After the database from the pivotal phase is locked, participants will be switched to an open-label dose of 150 mg canakinumab at their fourth scheduled extension visit (visit Month 9) (Figure 3-2). The patients will then start to receive one syringe of canakinumab 150 mg in 1 mL solution for injection.

No study drug treatment will be provided for those patients with both randomization and pivotal phase EOS prediabetes during the 6-month study drug washout period. This means that patients participating in the washout will skip two doses of their pivotal phase blinded assigned treatment arm. After the end of the study drug washout, participants will receive one dose of their assigned pivotal phase blinded treatment arm at their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3).

All participants of the extension phase will remain on the open-label dose of 150 mg canakinumab until the final dose of canakinumab is implemented at the study sites, based on the results from the pivotal phase.

5.2 Treatment arms

Following protocol Amendment 6 patients will be assigned to one of the following 4 treatment arms in a ratio of 1.4 : 1.3 : 1.3 : 2

- Canakinumab 50 mg s.c. at randomization (month 0), placebo s.c. at week 2 (month 0.5) , 50 mg s.c. at week 12 (month 3) and thereafter 50 mg s.c. quarterly
- 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

with allocation in a 1.3 : 0.7 : 1 ratio to 300 mg, 150 mg and placebo respectively in randomization plan A and 0.6 : 1.4 : 1 to 150 mg, 50 mg and placebo respectively in randomization plan B. All patients will be equally likely to be assigned to randomization plan A or B. Within each of the two randomization plans patients will have a 2:1 probability of being on active treatment. Prior to protocol amendment 6, patients were assigned in a 1:1:1

ratio to the 300 mg arm, the 150 mg arm or placebo. Across trial parts 1 and 2 this will approximately result in a 1:1:1:1.5 allocation to 300, 150, 50 mg and placebo, respectively. More precisely, given about 743 patients in trial part one and 9257 in trial part 2, the overall patient allocation would be approximately 2253 for both the 300 and 150 mg groups, 2160 for the 50 mg group and 3333 for the placebo group (a 1.01:1.01:0.97:1.5 ratio).

In the extension phase, all participants except for those with prediabetes will remain on their pivotal phase randomization plan and treatment arm for the first three extension phase visits (Month 0 to Month 6). The participants will be switched to a quarterly s.c. injection of an open-label dose of 150 mg canakinumab at their fourth scheduled extension visit (visit Month 9) following database lock of the pivotal phase (Figure 3-2). Prediabetic patients participating in the 6-month study drug washout will remain on their pivotal phase randomization plan and treatment arm only until their first visit of the subsequent main drug dispensing period (visit Month 0) before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3). All participants of the extension phase will remain on the open-label dose of 150 mg canakinumab until the final dose of canakinumab is implemented at the study sites, based on the results from the pivotal phase.

5.3 Treatment assignment

At pivotal phase 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.

In trial part 1 prior to the implementation of protocol amendment 6 at each site, there was a single randomization plan. In trial part 2 (following protocol amendment 6) this trial has two randomization plans A and B. The IVRS/IWRS randomly assigns patients to plan (A and B) and treatment. Randomization plan A includes placebo, 150 mg and 300 mg canakinumab arms and therefore, is fully blinded. Patients assigned to randomization plan A will receive two 1 mL injections at each trial visit except at visit 3 (1.5 months). Randomization plan B includes placebo, 50 mg and 150 mg canakinumab arms, and is also fully blinded. Patients assigned to randomization plan B will receive one 1 mL and one 0.5 mL injections at each pivotal phase visit except at visit 3 (1.5 months). 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.

In the extension phase all participants except for those with prediabetes will remain on their randomization number assigned at randomization in the pivotal phase until they switch to an

[redacted]

open-label dose of 150 mg canakinumab at the fourth scheduled extension visit (visit Month 9) (Figure 3-2). Prediabetic patients participating in the 6-month study drug washout will remain on their randomization number only until their first visit of the subsequent main drug dispensing period (visit Month 0) before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3).

Stratification

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

- Post MI ≥ 30 days but < 6 months
- Post MI ≥6 months

Sites will be asked to indicate the patients' glycemic status at the Visit 3 call post randomization as the Visit 1 and Visit 2 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 (5.6-6.9 mmol/L) inclusive at V1 or V2

  Note: To be included in the 6-month study drug washout, a patient must have a prediabetic status at both randomization and the pivotal phase EOS visit, according to the last HbA1c and FPG measurement available at the EOS visit
- T2DM: (patient needs to have one or more of the following)
  - HbA1c ≥ 6.5% OR FPG ≥ 126 mg/dL (≥7.0 mmol/L) at V1 and V2
  - Combination of HbA1c ≥ 6.5% and FPG ≥ 126 mg/dL (≥7.0 mmol/L) as confirmed at V1 and V2
  - Medical history of T2DM and on a current anti-diabetic medication

At the pivotal phase EOS visit sites will be asked to indicate the patients' glycemic status based on the last available lab results and based on the glycemic status at randomization. Patients who are determined to be prediabetic at both randomization and the pivotal phase EOS visit, will be included in the 6-month study drug washout (see Section 4 for definition).

Sites are required to call the IVRS/IWRS at every visit/phone contact to:

- Prescreen: Register the prescreening visit.
- 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. For randomization, enter patient's stratification as the time from the index MI to the date of randomization.
- Visit 3: Register the occurrence of the visit and provide glycemic status.
- 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 (pivotal phase).

[redacted]

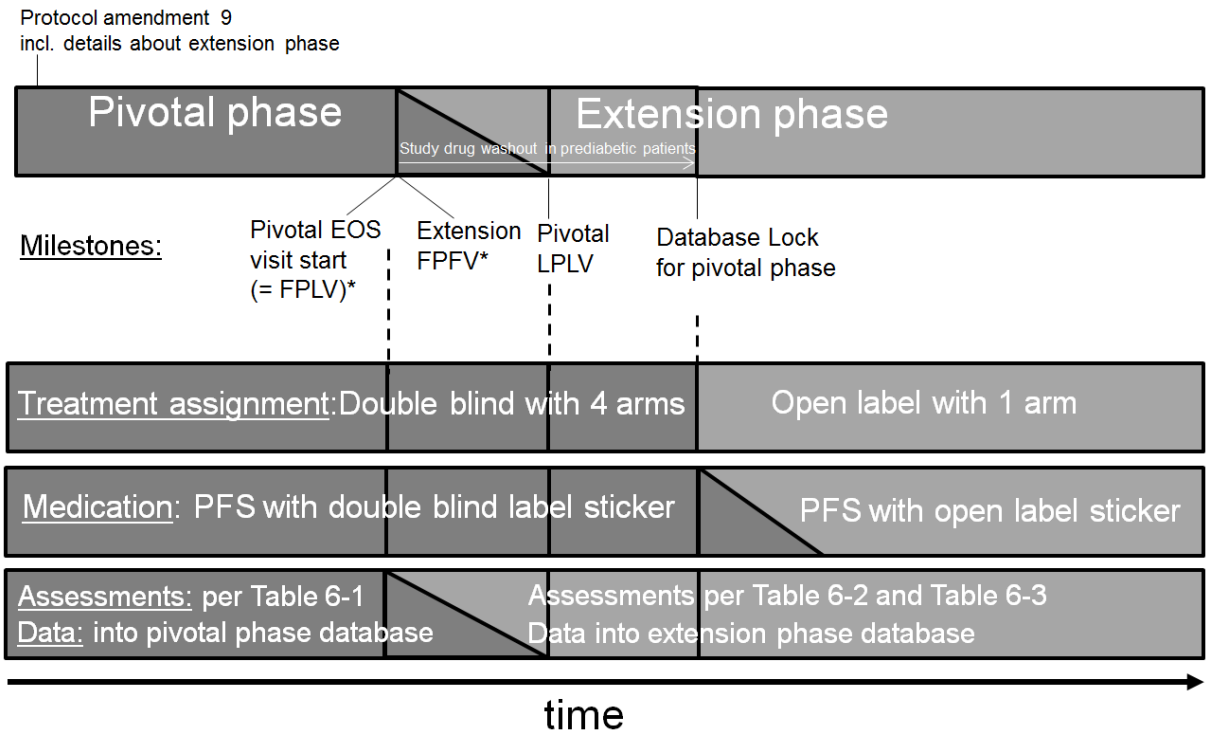
- Register a patient who has completed the pivotal phase (this will only occur when the study has been deemed complete by the DMC or Novartis and the patient returns for the pivotal phase EOS visit); register pivotal phase EOS visit as non-dispensing visit.
- Register a patient who has a glycemic status of "randomization and pivotal phase EOS prediabetes" and transitions into the 6-month study drug washout.
- End of Prediabetes Washout Visit 199: register a patient who has completed the 6-month study drug washout.
- Extension phase Visit 201 (Month 0): Register a patient who consented to participate in the extension phase.

  Register a drug dispensing visit, obtain medication numbers and provide study drug as per pivotal phase treatment arm assignment / randomization number. Note 1: The patients will remain on their assigned pivotal phase treatment arm until Visit 203 (Month 6) (Figure 3-2), except for prediabetic patients participating in the 6-month study drug washout. Such patients will remain on their assigned pivotal phase treatment arm only until Visit 201 (Month 0) (Figure 3-3). Note 2, for patients not participating in study drug washout: In case the last drug administration of the pivotal phase occurred within 4 weeks before the pivotal phase EOS visit, the study drug administration at Visit 201 (Month 0) will be skipped and the first injection as part of the extension phase will be performed at Visit 202 (Month 3).
- Extension phase Visit 202 (Month 3): prediabetic patient who completed the 6-month study drug washout will receive an open-label dose of 150 mg canakinumab and quarterly dispensing of an open-label dose of 150 mg canakinumab thereafter until the final canakinumab dose will be implemented at study sites based on the results from the pivotal phase (Figure 3-3). Patients who did not participate in the study drug washout will remain on their assigned pivotal phase treatment arm (Figure 3-2).
- Extension phase Visit 204 (Month 9): patient will receive an open-label dose of 150 mg canakinumab and quarterly dispensing of an open-label dose of 150 mg canakinumab thereafter until the final canakinumab dose will be implemented at study sites based on the results from the pivotal phase (Figure 3-2).
- Register a patient who has died or withdrawn consent during the extension phase.
- Register a patient who has completed the extension phase (when the patient returns for the extension phase EOS visit).

The randomization scheme for patients will be reviewed and approved by a member [redacted] The randomization codes will be maintained [redacted]

[redacted]

Figure 5-1 Transition from pivotal phase to extension phase



PFS: PreFilled Syringe, FPFV: First Patient First Visit, LPLV: Last Patient Last Visit

*for patients not participating in study drug washout: pivotal phase EOS visit and first extension phase visit are two different study visits that should occur on the same day. (If the last pivotal phase study drug injection before the EOS visit occurred within four weeks of the EOS visit, the first injection from the extension will be skipped). For participants of study drug washout: End of Prediabetes Washout visit and first visit of the main drug dispensing period of the extension phase are two different visits that should occur on the same day.

5.4 Treatment blinding

Patients, investigator staff and external personnel performing the assessments will remain blinded to the identity of the treatment from the time of randomization until the patients switch to the open-label dose of 150 mg canakinumab at extension phase visit Month 3 (only participants of 6-month study drug washout) and visit Month 9 (all patients who did not participate in the study drug washout), respectively. Data analysts will remain blinded to the identity of the treatment from the time of randomization until pivotal phase 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 and the bioanalyst and pharmacokineticist (to avoid the unnecessary analysis of placebo samples). These personnel will not be involved in any other trial activities.

The identity of the treatments in trial part 1 and in trial part 2 within each randomization plan (i.e., Plan A and Plan B) will be concealed by the use of double-dummy approach using study

[redacted]

drugs that are identical in packaging, labeling, schedule of administration and appearance. While investigators will not be blinded as to whether patients in trial part 2 are in randomization plan A or B, the probability of the patient being on active treatment is the same (2:1) in either case. Thus, it is not expected that this introduces any biases.

The study drug injections as part of the extension phase will remain blinded for the data analysts until pivotal phase database lock. The study drug injections received as part of the extension phase will remain blinded to patients, investigator staff and external personnel performing the assessments until patients switch to the open-label dose of 150 mg canakinumab at visit Month 3 (only participants of 6-month study drug washout; see Figure 3-3) and visit Month 9 (all patients not participating in study drug washout; see Figure 3-2), respectively. Until the switch to the open-label dose of 150 mg canakinumab during the extension phase, 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 pivotal study phase. 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.

During the open-label treatment as part of the extension phase, medication with a double blind label will continue to be dispensed until new supplies bearing open-label sticker are available at site. The dispensation of the open-label canakinumab dose during the extension phase with kits bearing a double blind label will be managed by the IVRS/IWRS.

[redacted] hsCRP (from baseline) 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

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

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.

The assigned patient numbers will be kept also during the extension phase.

[redacted]

5.5.2 Dispensing the study treatment

Each study site will be supplied by Novartis with study treatment in packaging of identical appearance per product volume. 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 four formulations provided (2 active and 2 corresponding 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.

For the main drug dispensing period of the extension phase, there will be a transition time. This transition time will be divided into three parts:

- First part from first visit (visit Month 0) until switch to open-label treatment with 150 mg canakinumab (i.e. visit Month 3 for participants of 6-month study drug washout (Figure 3-3), and visit Month 9 for all other patients (Figure 3-2)): Patients will continue to receive their double-blind treatment. The medication dispensing will be managed via IWRS/IVRS.
- Second part from first 150 mg canakinumab open-label treatment (i.e. visit Month 3 for participants of 6-month study drug washout and visit Month 9 for all other patients, respectively) until the final dose is implemented at study sites based on the results from the pivotal phase: Patients will receive 150 mg/1 ml canakinumab in an open-label fashion but with a double-blinded sticker until kits with the 150 mg dose are available at study sites with an open-label sticker. The medication dispensation will be managed via IWRS/IVRS.
- Third part from implementation of the final canakinumab dose at study sites until end of study: Patients will receive the final canakinumab dose with double-blinded sticker until kits with the appropriate dose are available at study sites with an open-label sticker. The medication dispensation will be managed via IWRS/IVRS.

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 at 2-8 degrees C (36-46 degrees F). Study treatment temperature should be verified and documented daily (business days) with a minimal / maximum thermometer or another equivalent temperature recording tool. 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.

[redacted]

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 Novartis monitor will arrange the return of all unused, damaged or expired study treatment and a copy of the completed drug accountability ledger to Novartis.

The above will also apply for the extension phase.

5.5.4 Instructions for prescribing and taking study treatment

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.

Instructions for use of the safety syringe can be found in Appendix 4.

During the extension phase, all participants except for those with prediabetes will remain on their pivotal phase assigned treatment arm for the first three visits (Month 0 to Month 6). The participants will be switched to an open-label dose of 150 mg canakinumab at the fourth scheduled extension visit (visit Month 9) (Figure 3-2) until the final dose of canakinumab is implemented at the study sites based on the results from the pivotal phase. During the open-label treatment with a dose of 150 mg canakinumab, only one injection will be administered per visit. Prediabetic participants of the 6-month study drug washout will receive one dose of their assigned pivotal phase blinded treatment arm at their first visit of the subsequent main drug dispensing period of the extension (visit Month 0) before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3) (Figure 3-3) until the final dose of canakinumab is implemented at the study sites based on the results from the pivotal phase.

5.5.5 Permitted 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 restart medication at any time during the study at the discretion of the investigator.

[redacted]

These changes must be recorded on the Dosage Administration Record CRF (eCRF).This will also apply for the extension phase.

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. Prior treatment for TB infection should be listed on the Concomitant Medications eCRF. Influenza vaccines administered two years prior to study start and pneumococcal vaccines administered five years prior to study start should be recorded on the Prior Influenza Vaccine eCRF and Prior Pneumococcal Vaccine eCRF, respectively. Vaccinations taken during the trial should be reported on the Concomitant Vaccination 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.

Also for the extension phase the investigator should instruct the patient to notify the study site about any new medications he/she takes after signing informed consent.

5.5.7 Prohibited treatment

Use of any treatments below is 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. This will also apply to the extension phase.

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 during the pivotal phase. During the extension phase, patients would still be required to be followed as per protocol to assess for any adverse events. 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 or intravenous steroids (> 20 mg prednisone orally daily for >14 days, > 5 mg orally prednisone daily, or equivalent dose of intravenous steroid) or high dose methotrexate (> 15 mg weekly). (Topical, inhaled, local steroid use in doses that are not considered to cause systemic effects are permitted.)
- Live vaccines within 90 days of study treatment.
  If a patient receives a live vaccine during this trial the next scheduled study treatment will be administered no earlier than 90 days from the administration of the live vaccine.

[redacted]

5.5.8 Interruption and Discontinuation of study treatment and premature patient withdrawal

The investigator should interrupt or 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 interrupts or 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. This will also apply to the extension phase.

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 and if the Investigator deems it appropriate to re-initiate study treatment. After the patient re-signs the ICF but prior to restarting study treatment, the Investigator must perform a thorough review of new medical histories and concomitant medication changes from the time corresponding to when the patient left the trial until he/she rejoined. New medical histories must be added to the Adverse Event eCRF and medication changes to the Concomitant Medication eCRF. Additionally, serum chemistry and hematology laboratory evaluations must be reviewed prior to resuming study treatment (Note: if serum chemistry and hematology results were obtained within 6 months prior to resuming study treatment, they do not need to be repeated at the central laboratory; if they are not available within 6 months a blood sample must be drawn and results reviewed by the Investigator prior to dosing the patient).
- Pregnancy. Patients must discontinue study treatment if pregnant; however, study treatment can be resumed in the future after consultation with the Sponsor providing the patient has stopped breast-feeding, has an appropriate clinical profile (i.e. safety laboratories, medical history, adverse events, concomitant medications) and there is documented evidence in the patient chart that the patient is of post-menopausal status per Section 4.2 Exclusion 2.
- Use of prohibited treatment as per Section 5.5.7
- Presence of any malignancy, other than excised basal cell skin carcinoma
- 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

[redacted]

- ALT or AST > 3x ULN with a T. Bilirubin > = 2x ULN but with no notable increase in ALP to > 2 X 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 > 48 hours

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). If subjects are rechallenged due liver function laboratory evaluations, they should be followed closely. The subject should be made aware of the potential risk, and consent to the rechallenge, and the Institutional Review Board (IRB) consulted.

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. This will also apply for the extension phase until patients switch to open-label administration of canakinumab starting at visit Month 3 (participants of 6-month study drug washout) and visit Month 9 (all patients not participating in study drug washout), respectively.

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 pivotal phase to assess for any potential study endpoints. The site will also attempt to obtain a vital status yearly during the extension phase. The patient contact information should be reviewed with the patient at every scheduled study visit to ensure it is up to date. If local regulations permit, the patient should be asked to provide the contact information for a friend or relative as well as their primary care physician (PCP).

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 and the patient should not be registered as discontinued in IVRS/IWRS unless they have withdrawn consent from all study follow-up. The patient should be encouraged to return for scheduled visits after discontinuation of study medication. If the patient refuses onsite visits, the patient, at minimum, should be encouraged to be followed by telephone per the assessment schedule, as every effort must be made by sites staff to follow patients for cardiovascular events and health status. For telephone visits, as much information should be collected as possible (vital status, study endpoints, adverse events, etc). If, at the end of study,

[redacted]

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, including telephone contacts to assess health status, 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.

The following will apply to the extension phase:

Patients may voluntarily withdraw from the study for any reason at any time. The patient contact information should be reviewed with the patient at every scheduled study visit to ensure it is up to date. If local regulations permit, the patient should be asked to provide the contact information for a friend or relative as well as their primary care physician (PCP).

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 and the patient should not be registered as discontinued in IVRS/IWRS unless they have withdrawn consent from all study follow-up. The patient should be encouraged to return for scheduled visits after discontinuation of study medication. If the patient refuses onsite visits, the patient, at minimum, should be encouraged to be followed by telephone per the assessment schedule, as every effort must be made by sites staff to follow patients for health status.

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. The

[redacted]

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, including telephone contacts to assess health status, 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.

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 dependable procedure in place to allow access to the IVRS/IWRS at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name
- patient number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in case of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time.

Any patient who is unblinded will continue in the study and may continue receiving study medication as per protocol. This also applies for the extension phase while patients are still on their assigned blinded treatment arm.

5.5.10 Study completion and post-study treatment

The study closeout will be initiated once the study has reached its primary endpoint of 1,400 patients with primary CV events. At this time point sites will be notified to bring back all

[redacted]

study patients for a pivotal phase EOS visit. At this time patients who have pivotal phase EOS status obtained will be deemed completed for the pivotal phase. 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 pivotal phase is deemed successfully completed (1,400 primary CV events reached) or is stopped by the DMC recommendation of overwhelming efficacy (prior to 1,400 primary CV events reached) or by Novartis the following will take place

- All patients with a glycemic status of prediabetes from both randomization and pivotal phase EOS visit will proceed into the 6-month study drug washout
- All other patients who continue to be eligible to receive study drug and consent to participate in the extension phase will continue study drug treatment. The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first. The extension phase is then deemed complete while safety follow-up is anticipated to be continued in registries following study results and discussion with Health Authorities.
- All patients with a glycemic status of prediabetes who completed the 6-month study drug washout and consent to participate in the main drug dispensing period of the extension phase will continue with the extension as noted above and restart study drug treatment.

5.5.11 Early study termination

Novartis is committed to follow the IHC Harmonized Tripartite Guidelines for Good Clinical Practice (GCP) in implementation of this trial. The sponsor can terminate the study prior to completion of the trial in the case of a probable negative risk-benefit balance. Furthermore, 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 of the pivotal phase 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

[redacted]

months for study assessments and quarterly for study treatment until notified by the site staff of pivotal phase completion. Only when the site staff has been notified of the pivotal phase completion by Novartis will the patients with a glycemic status of prediabetes from both randomization and pivotal phase EOS visit be asked to enter the 6-month study drug washout at their pivotal phase 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 (Visit 1). 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 (Note: centrally-performed hsCRP results must be obtained less than 60 calendar days prior to Visit 2 to be used to evaluate Inclusion criterion 5, Section 4.1). 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. Patients with a prescreen hsCRP $\geq$ 2 mg/L from the central laboratory do not require a second hsCRP at Visit 1, providing the prescreen hsCRP blood sample is drawn less than 60 days prior Visit 2 and the patient is on a stable (at least 4 weeks) long term (cardiovascular) medications.

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 elevated HbA_{1c} and/or FPG result to assess for conversion from pre-diabetes to T2DM.

[redacted]

Discontinuation of study treatment: It is highly encouraged that patients who discontinue study treatment 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 according to the visit schedule (i.e., every 3 months) to assess for any potential study endpoints and record as appropriately in the eCRFs.

For patients whose treatment is stopped as a result of a data monitoring committee recommendation to suspend treatment in one dose group, follow-up for cardiovascular (CV) and safety events will continue. Since these patients will not receive further study medication, less frequent follow-up will be conducted every 6 months.

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 pivotal phase please see Section 6.6.5 for details

Sites are required to call the IVRS/IWRS at the prescreening and screening visit and at each visit to register their patient's status and if applicable, receive the medication numbers to

[redacted]

dispense treatment. Dispensing of medication should be the last assessment performed at each visit.

[redacted]

Table 6-1 Assessment schedule of pivotal phase

Visit	Pre-Screen	1	2	2.5	3	4	5	6	7	8	9	10	11	12,16, 20,24[8]	13,17, 21, 25[8]	14,18, 22,26[8]	15,19, 23,27[8]	End of Study (EOS)
Month		-1	**0**	**0.5**	**1.5**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27,39, 51,63…**	**30,42, 54, 66…**	**33,45, 57,69…**	**36,48, 60,72…**	**event driven**
Obtain informed consent		X																
Prescreening Informed Consent	X																	
Height		X																
Inclusion/Exclusion		X																
Labs for entry criteria only:, HIV Screen, HBsAg and HCV antibody [For Japan only] [In Japan, HBc antibody and HBs antibody are additionally included]		X																
Hs-CRP	X[10]	X[7]	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/IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Administration			X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Prior & Concomitant Antidiabetic & CVD Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

Visit	Pre-Screen	1	2	2.5	3	4	5	6	7	8	9	10	11	12,16, 20,24[8]	13,17, 21, 25[8]	14,18, 22,26[8]	15,19, 23,27[8]	End of Study (EOS)
Month		-1	**0**	**0.5**	**1.5**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27,39, 51,63…**	**30,42, 54, 66…**	**33,45, 57,69…**	**36,48, 60,72…**	**event driven**
Efficacy Assessments																		
Potential endpoint assessment				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
Safety Assessments																		
Physical Exam			X						X				X				X	X
Vitals (includes BMI, weight, waist circumference)		X	X	X	X	X	X	X	X		X		X		X		X	X
ECG			X						X				X				X	X
Standard Hematology & Chemistry		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
[redacted]																		
Immunological (e.g. ANA) Screen			X															X[12]
[redacted]																		
AE (prompting for infections)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test in women[9]			X															X

[redacted]

Visit	Pre-Screen	1	2	2.5	3	4	5	6	7	8	9	10	11	12,16, 20,24[8]	13,17, 21, 25[8]	14,18, 22,26[8]	15,19, 23,27[8]	End of Study (EOS)
Month		-1	0	0.5	1.5	3	6	9	12	15	18	21	24	27,39, 51,63…	30,42, 54, 66…	33,45, 57,69…	36,48, 60,72…	event driven
Other																		
[redacted]																		

[redacted]

Visit	Pre-Screen	1	2	2.5	3	4	5	6	7	8	9	10	11	12,16, 20,24[8]	13,17, 21, 25[8]	14,18, 22,26[8]	15,19, 23,27[8]	End of Study (EOS)
Month		-1	0	0.5	1.5	3	6	9	12	15	18	21	24	27,39, 51,63…	30,42, 54, 66…	33,45, 57,69…	36,48, 60,72…	event driven

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

[2] Diagnosis of diabetes [redacted] 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. 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 a direct LDL cholesterol assay will be employed.

[redacted]

[5] Please see Section 6.6.4 and Section 6.6.5 for administration of the questionnaires in addition to the use of the modified Rankin questionnaire.

[redacted]

[7] Patients with a prescreen hsCRP ≥ 2 mg/L from the central laboratory do not require an hsCRP at Visit 1, providing the centrally-performed prescreen hsCRP is less than 60 days prior Visit 2 and the patient is on stable (at least 4 weeks) long term (cardiovascular) medication.

[8] 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

[9] Mandatory for all women, regardless of menopause or surgical history.

[10] The pre-screening hs-CRP value should be noted in the patient chart.

[11] Includes prior treatment for tuberculosis as well as prior flu and pneumococcal vaccinations and all concomitant vaccinations (Section 5.5.6)

[12] Upon approval by Novartis, the Investigator (in select countries) may collect EOS frozen blood samples prior (ideally within 3 months) to the scheduled EOS visit.

[redacted]

Table 6-2 lists all of the assessments of the extension phase for patients not participating in the 6-month study drug washout. The table 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 first drug administration as part of the extension phase will be performed at the first visit of the extension phase. The first visit of extension phase at Month 0 (visit 201) should occur on the same day as the pivotal phase EOS visit (Figure 3-2). In case the last drug administration of the pivotal phase occurred within 4 weeks before the pivotal phase EOS visit, the study drug administration at the extension phase Month 0 visit will be skipped and the first injection as part of the extension phase will be performed at the Month 3 visit (visit 202). If the pivotal phase EOS visit and the first visit of the extension phase cannot occur on the same day, the Investigator must perform a thorough review of new medical histories and concomitant medication changes from the time of the last trial visit until the first visit of the extension phase. New medical histories must be added to the Adverse Event eCRF and medication changes to the Concomitant Medication eCRF. After signing the ICF, the patient should enter the extension phase at the visit number corresponding to the visit that would be scheduled if the pivotal phase EOS visit and first visit of the extension phase occurred on the same day. However, if this visit number is greater than Month 9 (Visit 204), the patient should enter the extension phase at visit Month 9 (Visit 204). The first visit of the extension phase should occur within 18 months of the last visit of the pivotal phase. The visit assessments listed below are for the estimated timeframe a patient would participate in the study. The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first.

Discontinuation of study treatment: It is highly encouraged that patients who discontinue study treatment 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 according to the visit schedule (i.e. every 3 months) to assess for any adverse event and record as appropriately in the eCRFs.

Sites are required to call the IVRS/IWRS 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.

[redacted]

Table 6-2 Assessment schedule of extension epoch for patients not participating in study drug washout

Visit Number	201[2]	202	203	204[5]	205	206	207	208	209	210	299 (End of extension[1])
Month	0[2]	3	6	9	12	15	18	21	24	27	30[1]
Obtain informed consent	X										
Pregnancy test in women[3]	X[7]										X
Call IVRS/IWRS	X	X	X	X	X	X	X	X	X	X	X
Prior & Concomitant Antidiabetic & CVD Medications	X[6,7]	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X[6,7]	X	X	X	X	X	X	X	X	X	X
AE (prompting for infections, malignancies, CV events)[8]	X[6,7]	X	X	X	X	X	X	X	X	X	X
Drug administration	X[2]	X	X	X[5]	X	X	X	X	X	X	
Study phase completion form											X
[redacted]											
Vitals (includes BMI, weight, waist circumference)					X				X		X

[1] The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first.

[2] First visit of extension phase at Month 0 (Visit 201) should occur on the same day as the pivotal phase EOS visit. In case the last drug administration of the pivotal phase occurred within 4 weeks before the pivotal phase EOS visit, the study drug administration at the extension phase visit 201 (Month 0) will be skipped and the first injection as part of the extension phase will be performed at visit 202 (Month 3). Prior & Concomitant Antidiabetic & CVD Medications, Concomitant Medications, Vitals and AE assessment are not required at first visit of extension phase (Month 0, Visit 201) if they are performed as part of the pivotal phase EOS visit.

[3] Mandatory for all women, regardless of menopause or surgical history. Pregnancy test to be performed locally.

[redacted]

[5] Visit 204 (Month 9) will be the first scheduled visit at which an open-label dose of 150 mg canakinumab will be administered. The intermediate dose of 150 mg canakinumab will be administered until the final dose of canakinumab is implemented at the study sites based on the results from the pivotal phase.

[6] Adverse Events and Concomitant Medications ongoing from the pivotal phase EOS visit must be re-entered into the extension phase visit Month 0 (Visit 201) Adverse Event eCRF and Concomitant Medication eCRF, respectively.

[7] Adverse Events, Concomitant Medications and a urine pregnancy test will be newly assessed for patients who do not have the pivotal phase EOS visit on same day as the first visit of the extension phase.

[8] New medical histories must be added to the Adverse Event eCRF.

[redacted]

Table 6-3 lists all of the assessments of the extension phase for patients with prediabetic status at both randomization and pivotal phase EOS visit who participate in the 6-month study drug washout with no study drug administration. The table 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. During the study drug washout, prediabetic patients will skip two doses of their pivotal phase blinded assigned treatment arm. The pivotal phase EOS glycemic status will be assessed based on the last HbA1c and FPG data available at the EOS visit. If no HbA1c value is available from the End of Prediabetes Washout visit or if a diabetes diagnosis is only based on one FPG value of ≥ 126 mg/dL (≥ 7 mmol/L) from the End of Prediabetes Washout visit, an unscheduled visit should be conducted within 6 weeks. At their first visit of the subsequent main drug dispensing period of the extension phase (visit Month 0) study drug washout participants receive one dose of their assigned pivotal phase blinded treatment arm before they switch to the open-label dose of 150 mg canakinumab at their next visit (visit Month 3). The first visit of the main drug dispensing period of the extension phase (Month 0, Visit 201) should occur on the same day as the End of Prediabetes Washout visit (Visit 199) (Figure 3-3). If the End of Prediabetes Washout visit and the first visit of the main drug dispensing period of the extension phase cannot occur on the same day, the Investigator must perform a thorough review of new medical histories and concomitant medication changes from the time of the last attended trial visit until the first attended visit of the main drug dispending period of the extension phase. New medical histories must be added to the Adverse Event eCRF and medication changes to the Concomitant Medication eCRF. After signing the ICF, the patient should enter the main drug dispensing period of the extension phase at the visit number corresponding to the visit that would be scheduled if the End of Prediabetes Washout visit and first visit of the main drug dispensing period of the extension phase occurred on the same day. However, if this visit number is greater than Month 3 (Visit 202), the patient should enter the extension phase at visit Month 3 (Visit 202). The first visit of the main drug dispensing period of the extension phase should occur within 18 months of the last visit of the pivotal phase. The visit assessments listed below are for the estimated timeframe a patient would participate in the study. The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first.

Discontinuation of study treatment: It is highly encouraged that patients who discontinue study treatment 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 according to the visit schedule (i.e. every 3 months) to assess for any adverse event and record as appropriately in the eCRFs.

Sites are required to call the IVRS/IWRS 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.

[redacted]

Table 6-3 Assessment schedule of extension epoch for prediabetic patients participating in 6-month study drug washout

Visit Number	199[1] (End of Prediabetes Washout)	201[3]	202[8]	203	204	205	206	207	208	299 (End of extension[2])
Month	Pivotal phase EOS + 6 months	0	3	6	9	12	15	18	21	24[2]
Obtain informed consent		X								
Pregnancy test in women[4]		X								X
Call IVRS/IWRS	X	X	X	X	X	X	X	X	X	X
Prior & Concomitant Antidiabetic & CVD Medications	X		X	X	X	X	X	X	X	X
Concomitant Medications	X	X[9,10]	X	X	X	X	X	X	X	X
AE (prompting for infections, malignancies, CV events)[11]	X	X[9,10]	X	X	X	X	X	X	X	X
Drug administration		X	X[8]	X	X	X	X	X	X	
Study phase completion form	X									X
[redacted]										
Vitals (includes BMI, weight, waist circumference)	X			X				X		X
Physical Exam	X									
ECG	X									
hsCRP	X									
HbA1c & FPG	X[7]									
Standard Hematology & Chemistry	X									
Fasting Lipid Profile[6]	X									
[redacted]										

[redacted]

[1] Patients with prediabetic status as defined by HbA1c/FPG lab values of HbA1c of 5.7 – 6.4% or FPG of 100 – 125 mg/dL (= 5.6 – 6.9 mmol/L) at both pivotal phase randomization and pivotal phase EOS will participate in study drug washout before they restart study drug administration as part of the extension phase at visit 201 (Month 0), provided they sign the Informed Consent Form.

[2] The extension phase will continue in an individual country for a minimum of two years from the date of the first patients enrolled in that country. The maximum duration of the extension phase will be 2.5 years from the date of the first patient enrolled in that country or until marketed product is available in that country, whichever comes first.

[3] The first visit of the main drug dispensing period of the extension phase at Month 0 (Visit 201) should occur on the same day as the End of Prediabetes Washout visit (Visit 199). Prior & Concomitant Antidiabetic & CVD Medications, Concomitant Medications, Vitals and AE assessment are not required at visit Month 0 (Visit 201) if they are performed as part of the End of Prediabetes Washout visit (Visit 199).

[4] Mandatory for all women, regardless of menopause or surgical history. Urine pregnancy test to be performed locally.

[redacted]

[6] Patient must have fasted 10 hours for this test. 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 a direct LDL cholesterol assay will be employed.

[7] An unscheduled visit will be conducted within 6 weeks if no HbA1c value is available from the End of Prediabetes Washout visit (visit 199) or if a diabetes diagnosis is only based on one FPG value of ≥ 126 mg/dL (≥ 7 mmol/L) at the End of Prediabetes Washout visit.

[8] Visit 202 (Month 3) will be the first scheduled visit at which an open-label dose of 150 mg canakinumab will be administered. The intermediate dose of 150 mg canakinumab will be administered until the final dose of canakinumab is implemented at the study sites based on the results from the pivotal phase.

[9] Adverse Events and Concomitant Medications ongoing from the End of Prediabetes Washout visit must be re-entered into the extension phase visit Month 0 (Visit 201) Adverse Event eCRF and Concomitant Medication eCRF, respectively.

[10] Adverse Events and Concomitant Medications will be newly assessed for patients who do not have their End of Prediabetes Washout visit on the same day as the first visit of the main drug dispensing period of the extension phase.

[11] New medical histories must be added to the Adverse Event eCRF.

[redacted]

6.1 Information to be collected on screening failures

All patients where informed consent has been given for the pivotal phase (including screening failures), will have the Screening Phase Disposition, Demographics, Inclusion / Exclusion, Informed Consent and Adverse Event (if SAE data has been collected) eCRFs completed.

For screened patients who signed informed consent but are not randomized or entered into the next period 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 period 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 of the pivotal phase. 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.

This will also apply for the extension phase.

[redacted]

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 of the pivotal phase, 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.

In the extension phase no endpoints will be collected. MACE will be recorded as adverse events, using the Adverse Event eCRF. No adjudication of events will be performed during the extension phase. Reporting of Adverse Events is described in Section 7.

6.4.2 Secondary efficacy assessment (secondary objectives)

All the listed secondary efficacy assessments are for the pivotal phase only unless specified otherwise. 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

[redacted]

[redacted]

[redacted]

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. [redacted]

6.5 Safety

Safety and Tolerability Assessments

- Laboratory evaluations (performed during pivotal phase and prediabetes washout)
- Height, weight and waist circumference (performed throughout full study)
- Adverse events and serious adverse events, including cardiovascular events, malignancies, and infections (performed throughout full study)
- Discontinuation due to AEs (performed throughout full study)
- Hypoglycemia events (performed throughout full study)
- Injection site reactions (assessed throughout full study)
- Physical Exam (performed during pivotal phase and prediabetes washout)

[redacted]

- [redacted]
- Vitals (assessed throughout full study)
- ECG (performed during pivotal phase and prediabetes washout)

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. During the pivotal phase, these adverse events will be adjudicated by an expert adjudication committee to strengthen data quality and safety conclusions. No adjudication of events will be performed during the extension phase.

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.

Physical examination will also be performed during prediabetes washout but not during main drug dispensing period of the extension phase.

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 per the assessment schedule. 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. 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.

Vital signs will also be performed during the extension phase.

Clinically notable vital signs are defined in Appendix 1.

6.5.3 Height, weight and waist circumference

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

[redacted]

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.

Height, weight and waist circumference will also be performed during the extension phase.

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. All screening labs must be reviewed for completeness prior to randomization. Lab results that are missing or unavailable must be repeated prior to randomization.

[redacted]

Laboratory evaluations will also be performed during prediabetes washout but not during main drug dispensing period of the extension phase.

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.

Hematology will also be assessed during prediabetes washout but not during main drug dispensing period of the extension phase.

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 and there is no underlying etiology for the increase in CK), 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 Visit 1 for eligibility purposes.

Clinical chemistry will also be assessed during prediabetes washout but not during main drug dispensing period of the extension phase.

[For Japan only]

[In Japan, HBc antibody and HBs antibody will also be measured for Visit 1 eligibility purposes. This is not applicable for the extension phase.]

[redacted]

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.

Fasting Lipid profile will also be performed during the prediabetes washout but not during main drug dispensing period of the extension phase.

[redacted]

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.

ECG will also be performed during the prediabetes washout but not during main drug dispensing period of the extension phase.

6.5.6 Pregnancy and assessments of fertility

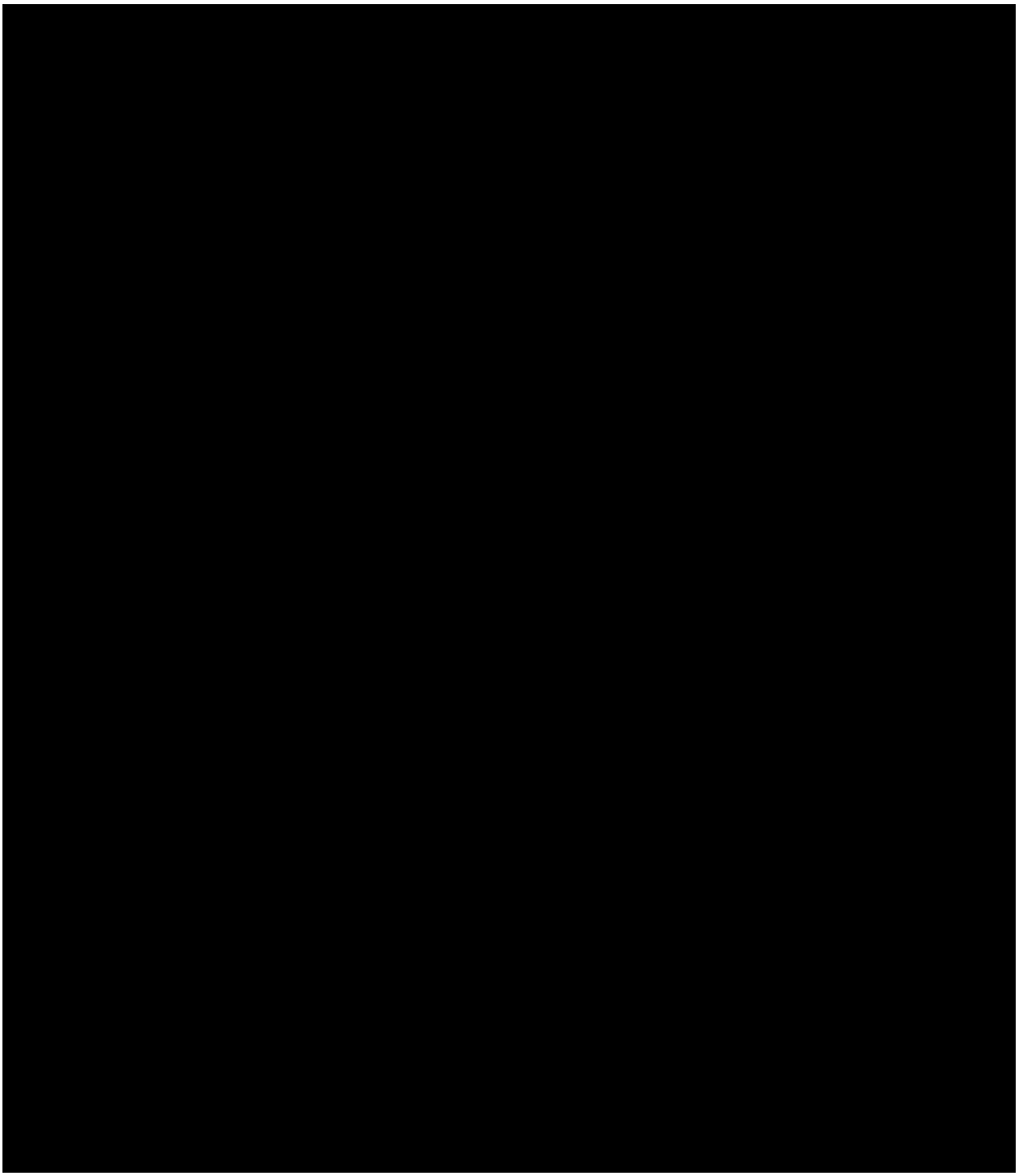
Neither the pivotal phase nor the extension phase include women of child bearing potential and therefore pregnancy test should be performed on all female study participants to detect unexpected pregnancies. A positive urine pregnancy test requires immediate interruption of study treatment until serum 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 restarted 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, serious infections and malignancies, will be adjudicated by two expert adjudication committees during the pivotal phase. No adjudication of events will be performed during the extension phase. Additionally, canakinumab and canakinumab antibody

[redacted]

concentrations will be measured during the pivotal phase due to the hypothetical risk of immune response to the study treatment. These safety events of special interest represent hypothetical risks of canakinumab treatment.



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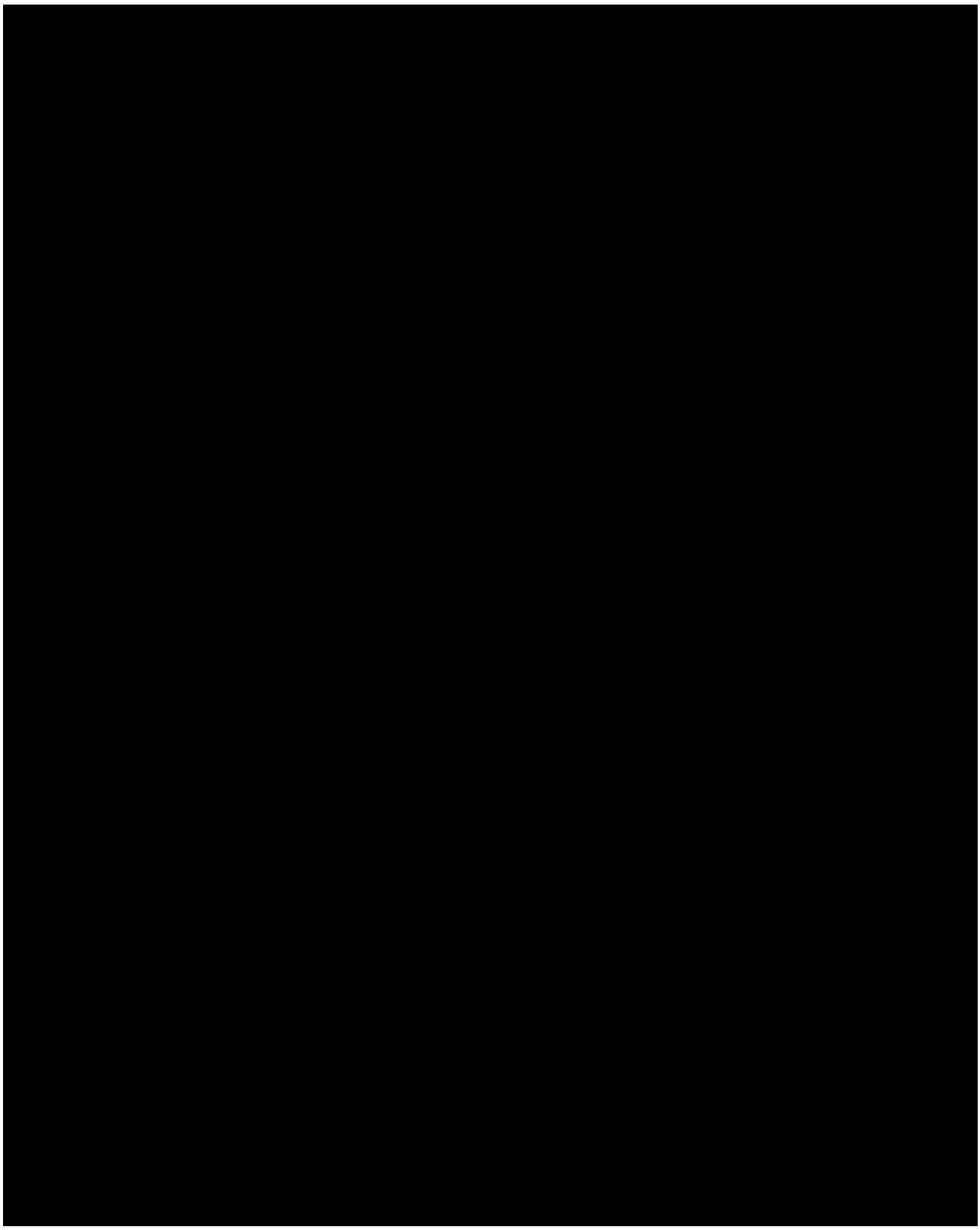

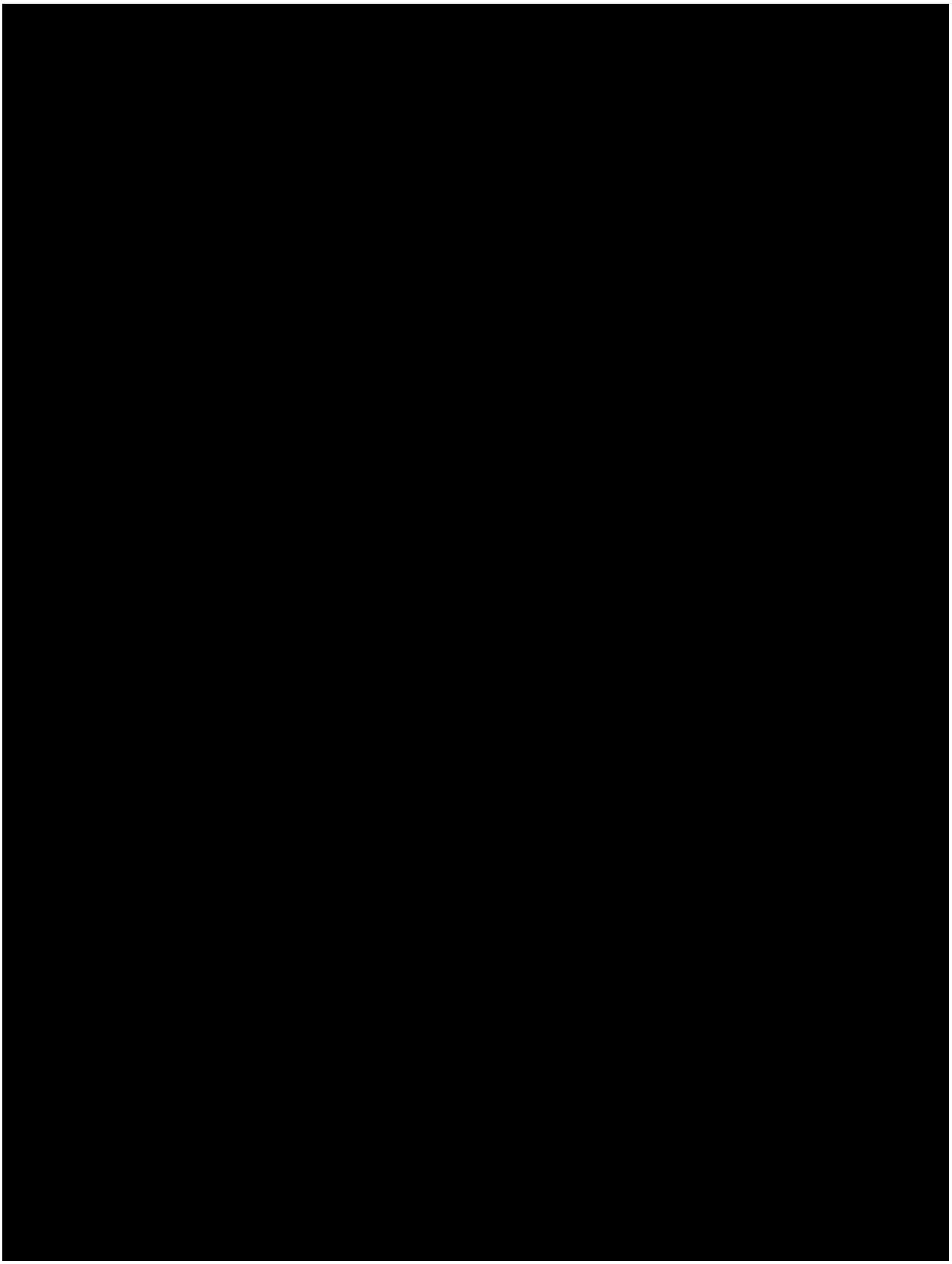

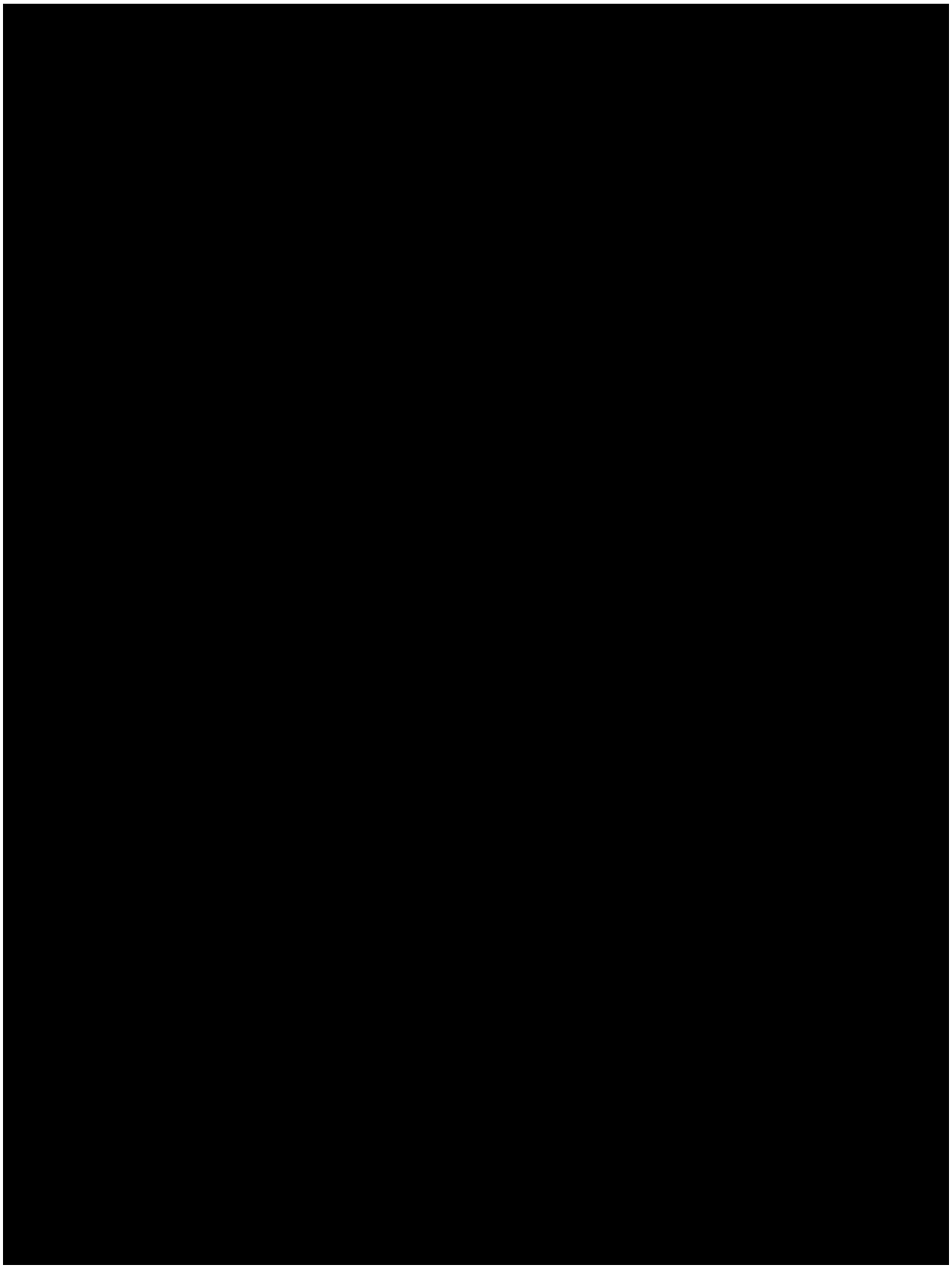

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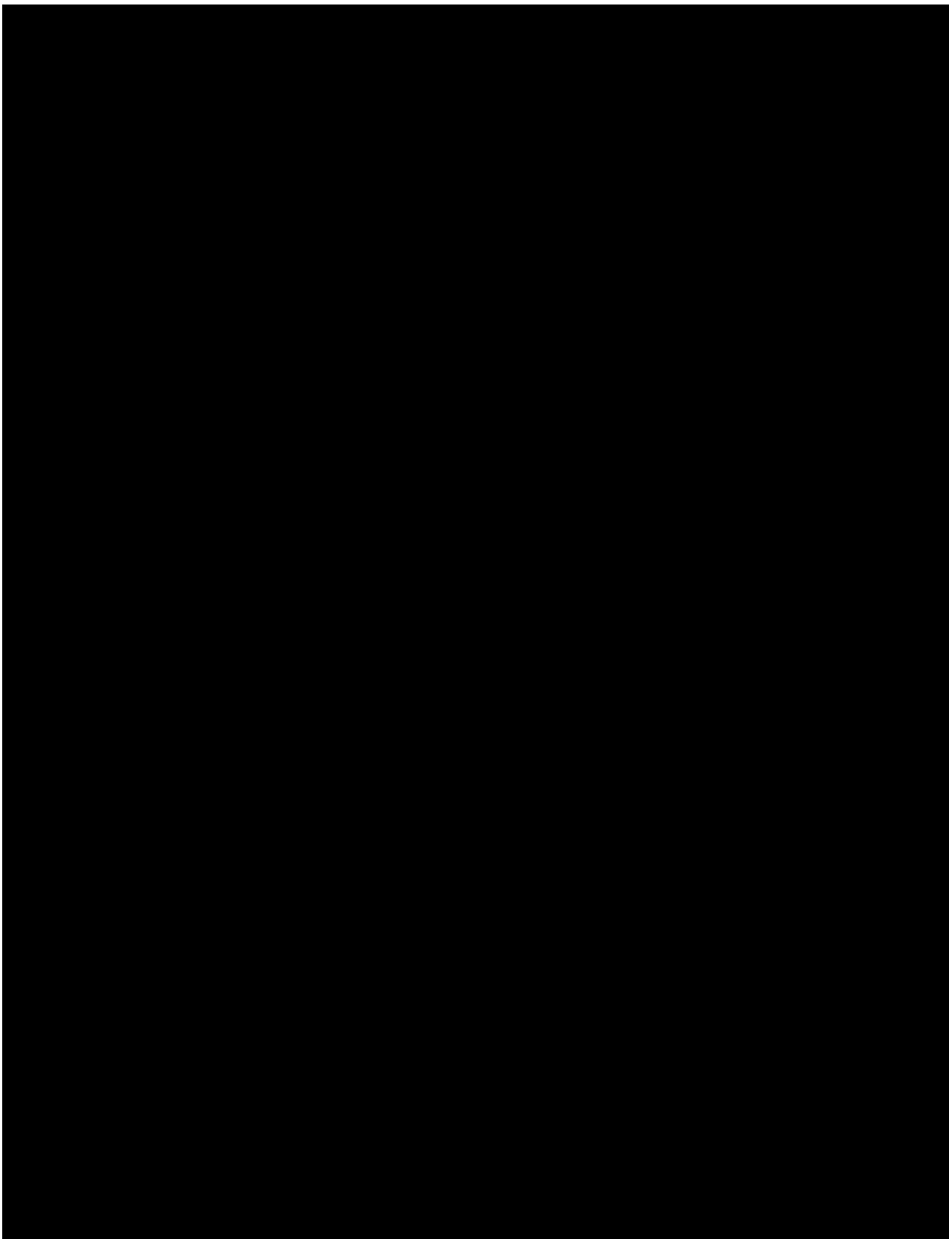

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7 Safety monitoring

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 must 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

During the pivotal phase all adverse events, which are no protocol endpoints, must be recorded on the Adverse Events CRF with the below listed information. During the extension

[redacted]

phase ALL adverse events 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 an 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
  - In CACZ885M2301, malignancies are considered medically significant. This classification will aid in the data collection on these events.

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

[redacted] any cardiovascular [redacted]

event sent for adjudication as a potential study endpoint or reported as a 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 the 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.

The study specific exemption does not apply to the extension phase. During the extension phase ALL adverse events will be reported as AEs following the procedures described in Section 7.1 and Section 7.2. No adjudication of events will take place during the extension phase.

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 reasonably 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 during the pivotal phase, 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.

[redacted]

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to study drug(s), complete the SAE Report Form in English and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information 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.

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 EU Guidance 2011/C 172/01 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 during pivotal phase

The integrity of the pivotal phase 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/CT12 Guideline (2006)). Therefore, in the pivotal phase, 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. During the pivotal phase, 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 the pivotal phase:

- 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)
- [redacted]
- [redacted]
- Hospitalization or prolongation of hospitalization for heart failure
- Critical Limb ischemia

[redacted]

- Limb amputation
- Transient Ischemia Attack (TIA)
- New onset type 2 diabetes (NOD)
- [redacted]
- Coronary angiography / Coronary Revascularization (PCI or CABG)
- [redacted]
- [redacted]

The Data Monitoring Committee (DMC) will review these endpoint data throughout the pivotal phase in an unblinded manner. Should the DMC make recommendations on the conduct of the pivotal phase 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, the event 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 during the pivotal phase 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 during the pivotal phase 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.

During the extension phase, endpoints will no longer be collected. The above described protocol exemption does not apply for the extension phase. During the extension phase ALL SAEs must be reported to Novartis within 24 hours of learning of the occurrence as outlined in Section 7.2.

[For Japan only]

[In Japan, the following pre-defined study endpoints must be reported to Novartis Pharma K.K within 24 hours of learning of the occurrence, using the "Japan Pre-defined Study

[redacted]

Endpoints Reporting Form". The detail of cases that need to be reported to Novartis Pharma K.K. and procedures for reporting are described in a separate document.

- [redacted]
- Hospitalization or prolongation of hospitalization for heart failure
- Critical Limb ischemia
- Limb amputation
- Transient Ischemia Attack (TIA)
- New onset type 2 diabetes (NOD)
- [redacted]
- Coronary angiography / Coronary Revascularization (PCI or CABG)
- [redacted]
- [redacted]

This will not apply to the extension phase.]

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 during the pivotal phase 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 the pivotal phase, 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 DURING PIVOTAL PHASE

- 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

[redacted]

- Opportunistic infections
- Systemic lupus erythematosus
- Hypoglycemia
- Torsade de pointes, Long QT syndrome
- Pancreatitis
- Drug interaction
- Rhabdomyolysis
- Seizure
- Guillain-Barre syndrome
- Progressive multifocal leukoencephalopathy (PML)

In case the cause of the death event is not listed above it will be reported as study endpoint only. If the death event is adjudicated as a non-CV death, the death event will be reported as serious adverse event.

Reporting of adverse events during extension phase

During the extension phase, endpoints will no longer be collected. The above described protocol exemption does not apply for the extension phase. Therefore ALL adverse events are collected as SAE's, as described in Section 7.2. During the extension phase ALL SAEs must be reported to Novartis within 24 hours of learning of the occurrence.

7.3 Reporting of study treatment errors including misuse/abuse

This section applies to the extension phase only.

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE

[redacted]

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with a SAE

7.4 Pregnancies

Women of child-bearing potential are excluded from this study (pivotal and the extension phases); 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.

7.5 Data Monitoring Committee

An external and independent DMC will be formed for the pivotal phase 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.

For the extension phase the DMC will not be utilized.

7.6 Adjudication Committees

There will be three separate adjudication committees for the pivotal phase. There will be no adjudication committees utilized for the extension phase.

7.6.1 Cardiovascular clinical events adjudication committee

During the pivotal phase, 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,

[redacted]

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 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 prediabetes drug washout period,
2. or the patient's entry into the main drug dispensing period of the extension phase,
3. or for those patients not proceeding to neither prediabetes washout nor the main drug dispensing period of the extension phase, the patient's pivotal phase end of study visit, but only if it occurred during the pivotal close-out period,
4. or otherwise the end of the pivotal 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 extension phase (including the prediabetes washout) should be reported as adverse events, as specified in Section 7.1 and Section 7.2.

Baseline and yearly ECG will be obtained during pivotal phase 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.

All unplanned hospitalizations except those related to planned procedures that are non-CV related will be reviewed for adjudication and adjudicated when data allows adjudication.

No cardiovascular clinical events adjudication committee will be utilized for the extension phase.

7.6.2 Infection Adjudication Committee

An independent Infection Adjudication Committee (IAC) has been formed on a program level and will review pertinent data from this pivotal trial.

The mission of the IAC is to independently and blindly review, evaluate and categorize new reports of pre-defined infections as they become available during the conduct of this trial. Members from the IAC may also adjudicate reports of serious allergies.

[redacted]

The members, detailed mission and procedures of the IAC are detailed in the IAC charter.

The IAC will not adjudicate cases from the extension phase.

7.6.3 Malignancy Adjudication Committee

An independent Malignancy Adjudication Committee (MAC) has been formed on a program level and will review pertinent data from this trial.

The mission of the MAC is to independently and blindly review, evaluate and categorize reports of malignancy events across all potential indications and therapeutic areas in the canakinumab development program. Members from the MAC may also adjudicate reports of serious allergies.

The members, detailed mission and procedures of the MAC are detailed in the MAC Charter.

The MAC will not adjudicate cases from the extension phase.

8 Data review and database management

8.1 Site monitoring

Before pivotal phase initiation, at an investigator's meeting and/or a site initiation visit, a Novartis or study team representative will review the protocol and (e)CRFs with the investigators and their staff. This review will not be repeated for the extension phase. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. 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. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyse data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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.

[redacted]

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Oracle Clinical/Remote Data Capture (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 on a regular basis 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.

This will also apply for the extension phase.

The pivotal phase data and the extension phase data will be collected in two separate databases in order to avoid any risk of unblinding of pivotal phase data and in order to guarantee a secure pivotal phase database lock while the extension phase is ongoing. The name of the extension phase database and of some extension phase related documents will contain an identifier added to the study number CACZ885M2301.

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). Beyond the assessments during the study drug washout in prediabetic patients, no laboratory samples will be generated during the extension phase.

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO). Beyond the assessments during the study drug washout in prediabetic patients, no ECG will be generated during the extension phase.

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).

[redacted]

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 pivotal phase (i.e. excluding the extension phase with the study drug washout in prediabetic patients, 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 [redacted]

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.This will also apply for the extension phase until patients switch to the open-label canakinumab dose.

[redacted]

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.

[redacted]

- **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/IWRS 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.

Analyses will take into account the changes in randomization between trial part 1 and trial part 2 (e.g. by stratifying analyses by trial part) and that patients in trial part 2 were not recruited concurrently with those in trial part 1. This ensure no biases arise e.g. due to differences over time (and thus between the two trial parts) in the recruited patient population or background medical care. Unless otherwise specified, patients randomized to the same treatment arm under randomization plan A or B will be analyzed together. This is not believed to introduce any biases with respect to the assessment of endpoints and the standard or care provided to patients, because patients have an equal 2:1 chance of being on an active treatment group under either randomization plan. Thus, it is not considered necessary to also stratify analyses in this respect.

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, as well as by trial part. 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, as well as by trial part. 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 overall and by trial part.

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 by trial part 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

[redacted]

- 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
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - 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 stratified by trial part and time since index MI for the categorical variables and the F-test for the continuous variables as appropriate. These p-values will be provided for descriptive

[redacted]

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 randomized treatment received during the double-blind pivotal phase 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 pivotal phase completion visit during the pivotal phase 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 trial part and 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 and full analysis set in separate tabulations by trial part 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

[redacted]

- 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/[redacted] 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 period of the pivotal phase. This means that only events between a patient's randomization and the first of either

1. the patient's entry into the prediabetes washout period for prediabetic patients,
2. or the patient's entry into the main drug dispensing period of the extension phase,
3. or for those patients proceeding to neither washout nor main drug dispensing period of the extension phase, the patient's end of pivotal phase visit, but only if it occurred during the pivotal phase close-out period,
4. or otherwise the end of the pivotal phase 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 in the pivotal phase. 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 in the pivotal phase.

[redacted]

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 300 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 150 mg dose group is greater than or equal to the hazard rate of the placebo group
- H_{31}: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 50 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) and by trial part using exact method for handling ties on the full analysis set (FAS) according to the intent-to-treat principle. The stratification according to trial part entails some statistical inefficiency compared to a trial that would have had 4 treatment groups from the start, especially for the 50 mg dose. However, this approach ensures that no biases arise e.g. due to differences over time between the two trial parts in the recruited patient population or background medical care. While investigators are not blinded to the assignment of patients to randomization plan A or B, this is not believed to introduce any biases with respect to the assessment of the primary endpoint and the standard or care provided to patients, because patients have an equal chance of being on an active treatment group under either randomization plan. Thus, it was not considered necessary to also stratify the analysis in this respect, but a sensitivity analysis will be conducted. A sensitivity with respect to the consistency of treatment effects in the two parts of the trial will also be performed.

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. (Bretz, et al. 2009); however, in intersection null hypotheses involving the primary null hypotheses for the 300 mg, 150 mg or 50 mg doses these primary null hypotheses will be tested using a weighted version of Dunnett's test (Dunnett 1955). Specifically this means that for any intersection hypothesis from the full closure that contains at least two of H_{11}, H_{21} and H_{31}, a weighted Dunnett test amongst the primary null hypotheses is performed with the overall significance level for that test and the weighting chosen according to the weights assigned to these null hypotheses by the update algorithm of the graphical method. The nominal adjusted significance levels based on the weighted Dunnett test are always slightly larger than the corresponding Bonferroni levels would be. For example the mvtnorm package in R (Genz and Bretz 2009) calculates the nominal Dunnett significance levels at the final analysis for the 300 mg, 150 mg and 50 mg doses versus placebo in the test of the global null hypothesis to be 0.5500504%, 1.1001008% and 1.1001008%, respectively, as compared to Bonferroni levels of 0.49%, 0.98% and 0.98%. If other non-primary null hypotheses in such an intersection hypothesis have non-zero weight on the basis of Figure 9-1, the intersection null hypothesis will be rejected if either (a) these other null hypotheses can be rejected at a Bonferroni significance level based on that weight or (b) the primary null hypotheses can be rejected based on the weighted Dunnett test. All other intersection hypotheses are tested with

[redacted]

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.

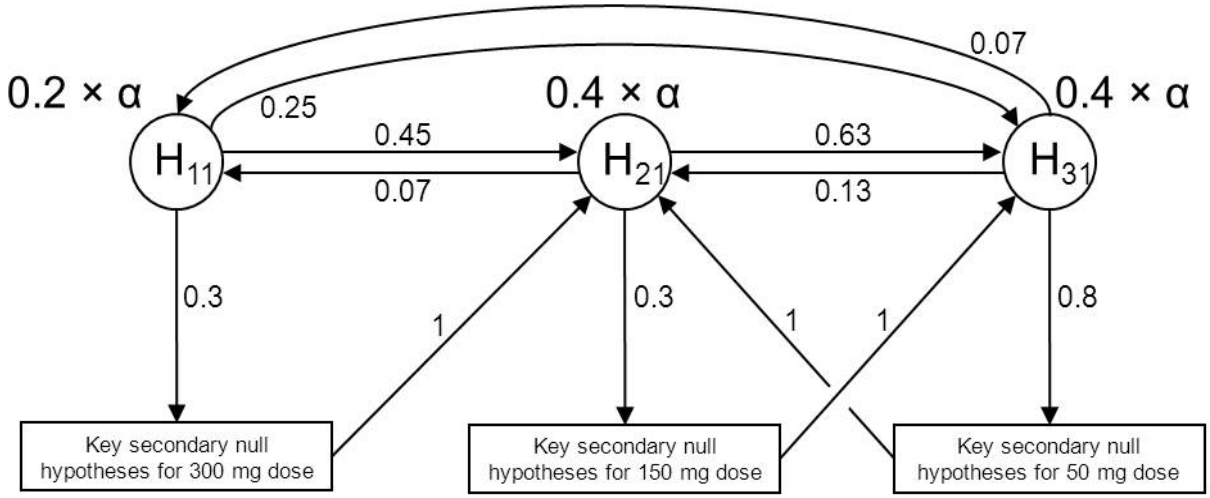
The testing procedure in Figure 9-1 initially splits the entire available significance level (at the final analysis 2.45%) between the three primary null hypotheses relating to the three doses (at the final analysis 20% of 2.45% = 0.49% for the primary null hypothesis of the 300 mg dose, 40% of 2.45% = 0.98% for that of the 150 mg dose and 40% of 2.45% = 0.98% for that of the 50 mg dose). These weights were chosen by balancing the prior expectations about the efficacy dose response relationship versus the potential for a better risk benefit ratio with lower doses. In particular, one aim was to ensure that there would be at least 80% power for the 50 mg dose to become significant assuming a 20% relative risk reduction for all doses. In the process of ensuring this, the weight for the 300 mg dose was reduced more than that of the 150 mg, because a higher dose is only of interest if it demonstrates a better efficacy than lower doses. This means that when the other doses are not effective the 300 mg dose would only become significant with a relative risk reduction that is at least in the region of 17.5%, while for the 150 mg dose this would already be the case with relative risk reductions below 16%. However, this was considered acceptable in order to ensure the desired operating characteristics for the 150 mg and 50 mg dose.

Key secondary endpoints for a dose are tested using a weighted Bonferroni-Holm procedure (Holm 1979) only after successful rejection of the primary null hypothesis for that dose. In that case, a higher fraction of the local significance level that is passed from the primary null hypothesis for a dose to the key secondary endpoints for the same dose is assigned to the secondary CV composite endpoint (90%) than to the new onset of diabetes endpoint (10%).

Note that if the primary endpoint for the 300 mg dose (null hypothesis H_{11}) is rejected 45% of the local significance level assigned to that null hypothesis is shifted to the primary endpoint for the 150 mg dose (null hypothesis H_{21}) and 25% to the primary endpoint for the 50 mg dose (null hypothesis H_{31}). This reflects the possibility that lower doses could potentially have a better safety profile than higher doses; hence, it would be desirable to demonstrate the efficacy of lower doses even after demonstrating the efficacy of a higher dose. In contrast, the main reason why some of the local significance level assigned to lower doses is shifted to higher doses is to preserve the consonance of the test procedure; i.e. to avoid a situation in which e.g. the primary null hypothesis for the 300 mg would be rejected by the weighted Dunnett test, but could not be rejected by the chosen closed testing procedure due to insufficient alpha being assigned to some intersection null hypotheses.

[redacted]

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



When the primary null hypothesis for a dose is rejected, some of the local significance level assigned to that primary null hypothesis is passed to the key secondary null hypotheses for the same dose. These are then tested using a weighted Bonferroni-Holm procedure at the available local significance level with weights of 90% for the key secondary CV composite and 10% for the key secondary new onset of diabetes endpoint. Only if both key secondary null hypotheses for a dose are rejected, will any of the local significance level assigned to these null hypotheses be passed on to null hypotheses for other doses.

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 1,400 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. An additional futility analysis may also be conducted by the DMC prior to the first planned efficacy IA (at approximately 50% primary events), but only after a sufficient number of primary events are accrued, i.e, >25%.

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 $\alpha = 2.5\%$. This constitutes an equivalent level of evidence as the two-sided 5% level. Multiplicity adjusted p-values will be calculated for each null hypothesis as the smallest significance level at which one can reject that null hypothesis. Both one-sided and two-sided p-values will be reported. To obtain the latter, the same test procedure as shown in Figure 9-1 will also be conducted in a one-sided fashion on the 2.5% significance level to test for the superiority of placebo over each test arm.

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) and by trial part using treatment (canakinumab doses and placebo) as a factor in the model using exact method for handling ties. Kaplan-Meier type plots will be presented to summarize the time to first event in the composite endpoint, by presenting the time-dependent

[redacted]

cumulative frequency and percentage of patients who reach the primary composite endpoint by treatment group. Appropriate methods for plotting the overall data from both trial parts together will be pre-specified in the statistical analysis plan. Separate Kaplan-Meier plots by trial part will also be provided.

Should one of the three 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. For patients whose treatment is stopped as a result of a data monitoring committee recommendation to suspend treatment in one dose group, follow-up for cardiovascular (CV) and safety events will continue. Since these patients will not receive further study medication, less frequent follow-up will be conducted every 6 months. Continued follow-up would likely enhance understanding of the safety of the other dose groups as well. Follow-up will simply continue in all scenarios until 1,400 patients have had a primary endpoint and the only difference to the pre-planned study conduct will be that the patients in the stopped treatment arms are not being treated after the DMC decision point.

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 pivotal phase. 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 pivotal phase 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 pivotal phase close out, the censoring date will be the final visit date,
- otherwise the censoring date will be based on the last pivotal phase 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 pivotal phase visit will be used, if the last known date the patient was alive is missing the date of the last pivotal phase visit at which it was known whether the patient experienced any clinical events since the last pivotal phase 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.

[redacted]

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 pivotal phase 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.

The three pooled canakinumab doses will be compared to placebo on the primary composite endpoint and its components, because in case of similar efficacy on all three doses this would be the most powerful test of the scientific hypothesis addressed by this trial. Additionally, when all three doses have similar efficacy such a pooled analysis approach may be able to provide the most precise information on the effects in subgroups. Methods to evaluate dose response in terms of cardiovascular events will also be pre-specified in the detailed statistical analysis plan.

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.

A sensitivity analysis will be conducted using randomization plan as an additional covariate or stratification factor in the primary model. A sensitivity with respect to the consistency of treatment effects in the two parts of the trial will also be performed. Finally, in order to achieve approximately 50% of patients < 12 months or ≥ 12 months post index-MI recruitment in one of these subgroups may be stopped earlier than in the other subgroup. If that occurs, then a sensitivity analysis stratifying the primary analysis by time since index MI 30 days to < 6 months, ≥ 6 months to <12 months and ≥ 12 months will be performed.

[redacted]

9.5 Analysis of key secondary [redacted] variables

Unless otherwise specified all time-to-event analyses will be based on events occurring during the double-blind period of the pivotal phase (see Section 9.4). Dose response in secondary [redacted] variables such as hsCRP will also be explored.

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 300 mg dose versus placebo

- H_{12}: The hazard rate of first adjudication committee confirmed secondary composite CV endpoint in the canakinumab 300 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 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 canakinumab 300 mg dose group than in the placebo group. The corresponding hypotheses for the comparison of the canakinumab 150 mg dose versus placebo are H_{22} for the secondary composite CV endpoint and H_{23} for the new onset of diabetes endpoint; the corresponding hypotheses for the comparison of the canakinumab 50 mg dose versus placebo are H_{32} for the secondary composite CV endpoint and H_{33} 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 and trial part. The hazard ratios will be estimated using a Cox regression model stratified by time since index MI and trial part. Kaplan-Meier type plots showing each treatment will be provided overall and separately by trial part. The multiplicity adjustment used to protect the familywise type I error rate is shown in Figure 9-1. Based on this testing procedure, once the primary null hypothesis for a dose has been rejected the key secondary endpoints for that dose are tested using a weighted Bonferroni-Holm test (Holm 1979) at the available local significance level for the key secondary endpoints for that dose. The weighting of this Bonferroni-Holm procedure will be 90% for the key secondary CV composite and 10% for the key secondary new onset of diabetes endpoint.

The secondary efficacy variable corresponding to new onset diabetes in patients with prediabetes at randomization will be the time from randomization to the first of repeated FPG ≥126 mg/dL (≥7.0 mmol/L) 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

[redacted]

of the time points when new onset of type 2 diabetes can be determined, events identified at the same pivotal phase visit time point for different patients will be considered as tied events and 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 pivotal phase 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 and trial part. The hazard ratios will be estimated using a Cox regression model stratified by time since index MI and trial part. Kaplan-Meier plots showing each treatment will be provided overall and by trial part. Patients who did not die will be considered censored at the last time they were reported to be alive.

Analysis of the prediabetes washout period

Data from the double-blind period of the pivotal phase and the prediabetes washout period of the extension phase will be combined to assess to what extent canakinumab truly delayed progression to diabetes and to what extent it only masked diabetes during the pivotal phase double-blind period. The analysis will take into account that masking of diabetes may have occurred in patients not diagnosed as diabetic during the pivotal phase 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.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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.

As appropriate overall (i.e. across the two trial parts) absolute risk differences, risk ratios, hazard ratios or odds ratios for each active dose versus placebo will be calculated taking into account the trial part to avoid any confounding of the safety assessment through differential follow-up or differences in patient populations.

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.

Adverse events (AEs) excluding trial endpoints

The incidence of treatment emergent AEs (events started on 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 for the pivotal phase will be summarized by primary system organ class (SOC), preferred term and also by severity and relationship to study treatment. Standardized MedDRA Queries (SMQs) may 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.

[redacted]

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

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

Similar summaries will be provided for the extension phase.

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. For the extension phase no adjudication of AEs will be performed.

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 for the pivotal phase:

- 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.

[redacted]

- 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.

[redacted]

[redacted]

[redacted]

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

[redacted]

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.

The observed blinded event rate at the time of protocol amendment 8 appears to be at the upper end of the previously expected range despite a lower than expected enrollment into the <6 month and <12 month post-index MI subgroups. The blinded event rate also appears to be stable over time into the second year of follow-up based on the current follow-up information (on average less than a year and up to 2.5 years in the first patients enrolled).

Needed number of patients with primary endpoints and Sample size

As shown in Table 9-1 1,400 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 all doses have a true 20% net relative hazard reduction compared to placebo for MACEs after discounting for discontinuations of treatment. Additionally, in this case both the 150 mg dose and 50 mg dose have ≥ 80% power to become significant.

Table 9-1 Power at the final analysis for 1,400 patients with a MACE

True relative risk reduction			Power [%]				
300 mg [%]	150 mg [%]	50 mg [%]	**at least one dose significant**	300 mg	150 mg	50 mg	all doses significant
25.0	25.0	25.0	**99.4**	93.5	96.1	96.3	89.0
22.5	22.5	22.5	**97.9**	85.4	90.4	91.4	76.5
20.0	20.0	20.0	**93.6**	72.0	80.6	80.3	56.9
17.5	17.5	17.5	**83.7**	54.9	65.8	63.9	35.8
22.5	22.5	0	**94.9**	82.3	88.1	1.9	1.9
20.0	20.0	0	**87.5**	67.6	77.2	1.8	1.8
22.5	17.5	10.0	**89.0**	81.6	64.9	24.7	20.9

Power results are based on 5,000 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 either the 150 mg dose would need to achieve a relative risk reduction of 15 to 16% versus placebo, or the 300 or 50 mg dose would need to achieve a relative risk reduction of 17 to 18% versus placebo in order for any dose to become significant. Once that is the case relative risk reductions of approximately 14 to 16% may become significant for the other doses.

A sample size of approximately 10,000 randomized patients is expected to be sufficient to accrue the planned number of 1,400 patients with a MACE in approximately 6 years. Given a 20% relative risk reduction in all active treatment arms, reducing the sample size from 17,200 patients to approximately 10,000 randomized patients reduces the expected number of patients with events in the 50 mg dose by less than 4% (11 patients with an event). Thus, the impact of the reduction in sample size on the power for the 50 mg dose will be negligible.

[redacted]

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.

No sample size calculation was performed for the extension phase, because the objective of the extension phase is long-term safety assessment in participants of the pivotal phase.

9.7 Power for analysis of key secondary variables

The revised sample size following amendment 6 was determined solely based on the primary endpoint, the initial calculations for the power of the key secondary variables were therefore not updated.

9.8 Interim analyses

Interim analyses of efficacy, futility and safety will be carried out during the pivotal phase of 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. One additional futility analysis may also be performed earlier than first planned efficacy IA (at approximately 50% primary events), but only after a sufficient number of primary events are accrued, i.e., >25%. 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.

This will also apply for the extension phase.

[redacted]

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.

[redacted]

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.

The informed consent form will be updated to include details of the extension phase. Patients may only be included in the main drug dispensing period of the extension phase (Visit 201 and beyond) after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent as described above.

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

[redacted]

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.

The above will also apply for the extension phase. The extension phase will be introduced via a protocol amendment. The informed consent form will be amended accordingly.

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.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal Standard Operating Procedures (SOPs), and are performed according to written Novartis processes.

This will also apply for the extension phase.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations during the pivotal and extension phases. 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

[redacted]

cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

This will also apply for the extension phase.

[redacted]

12 References

References are available on request.

Internal Reference Section

Investigator's Brochure, Edition 15 dated 09 August 2016

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[redacted]

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

[redacted]

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, [redacted]

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.

[redacted]

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:
- $\geq$ 0.2 mV in men or $\geq$ 0.15 mV in women in leads V2-V3 and/or $\geq$ 0.1 mV in other leads.

[redacted]

- 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:

[redacted]

- 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 ≥ 0.02 seconds or QS complex in leads V2 and V3
- Q-wave ≥ 0.03 seconds and ≥ 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 ≥ 0.04 seconds in V1-V2 and R/S ≥ 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, [redacted]. A second sample should be obtained 3-6 hours later. Recurrent infarction is diagnosed if there is a ≥ 20% increase of the value in the second sample. This value should exceed the 99th percentile URL. [redacted], there must also be documentation of decreasing values (two samples at least 6 hours apart) prior to the suspected new MI. [redacted]

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 ≥ 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.

[redacted]

- 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

[redacted]

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

[redacted]

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

[redacted]

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

[redacted]

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."

[redacted]

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 ($\geq$7.0 mmol/L) 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 ($\geq$7.0 mmol/L) followed

[redacted]

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.

[redacted]

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

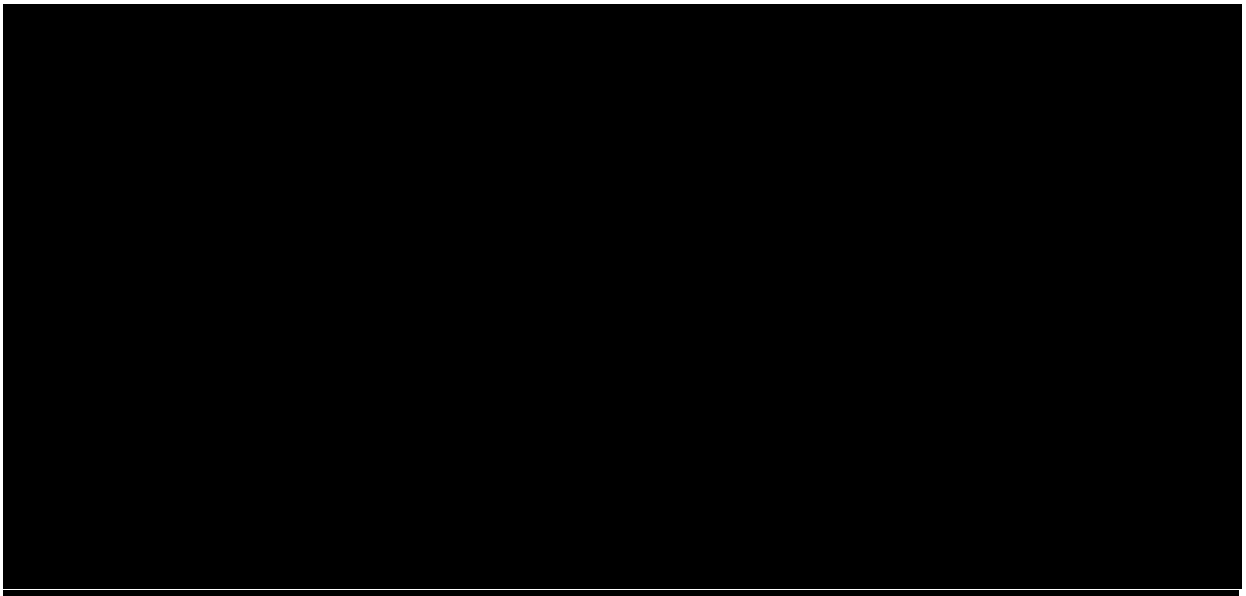
Procedure

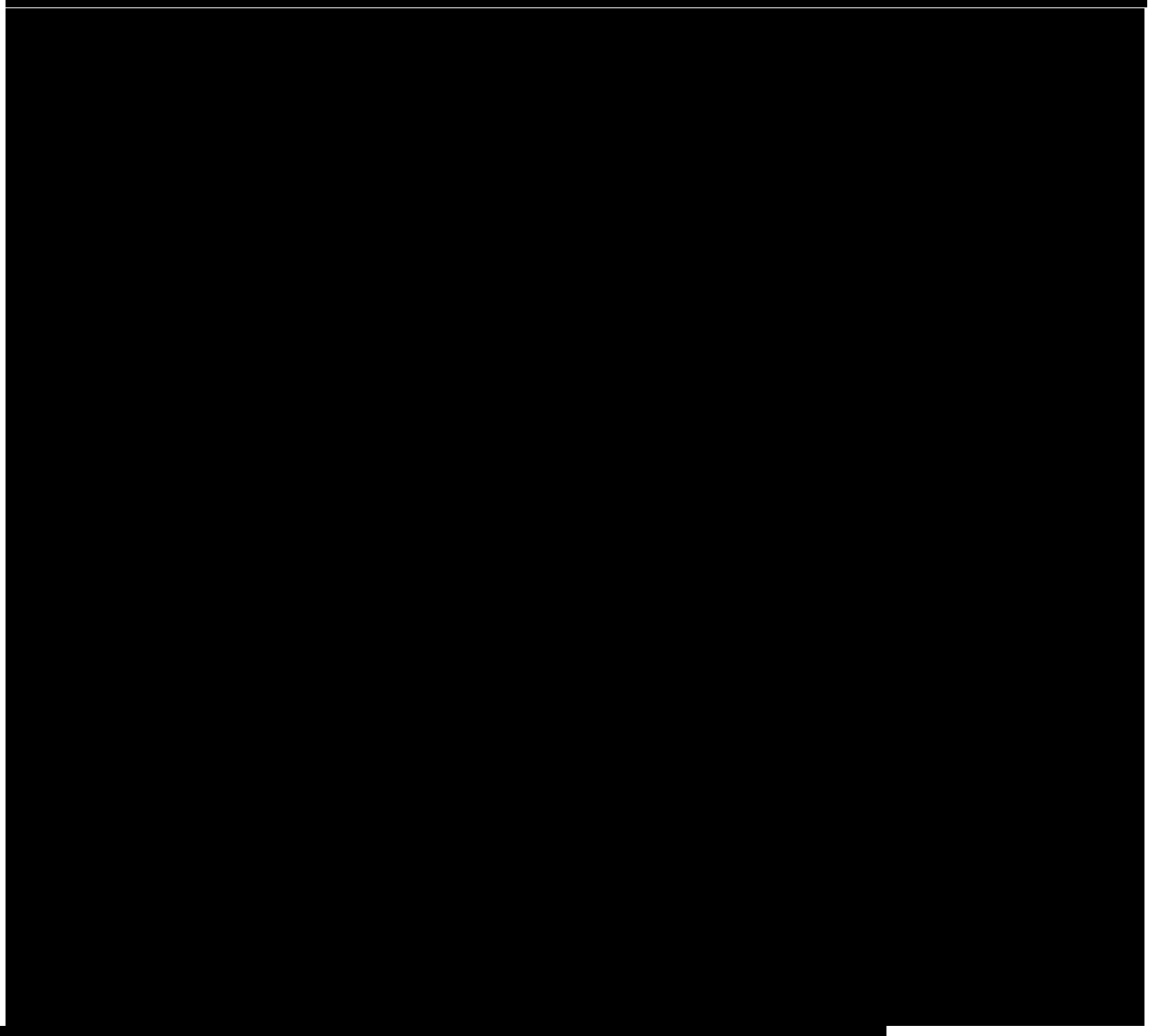
Therapeutic resection of the pathologic extremity. Reasons for amputation:

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

[redacted]

[redacted]





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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.

[redacted]

[redacted]

16 Appendix 4 Instructions for use of the safety syringe

Before using the safety syringe, please read the following information carefully. The box contains pre-filled safety syringe(s) individually sealed in a plastic wrapper.

Important safety information

Caution: Keep the safety syringe out of the reach of children.

1. Do not open the sealed outer box until you are ready to use the safety syringe.
2. Do not use the safety syringe if either the seal on the outer box or the plastic wrapper is broken, as it may be not safe for you to use.
3. Never leave the safety syringe lying around where other might tamper it.
4. Be careful not to touch the Safety Fingers at any time. By touching them, the safety syringe may self-activate.
5. Do not remove the needle cap until just before you give the injection.
6. The safety syringe cannot be re-used. Dispose of the used safety syringe immediately after use in a sharps container OR according to the regulatory needs of your country.

Storage of the safety syringe

1. Store the safety syringe sealed in its outer box in the refrigerator between 2°C and 8°C (36°F and 46°F). DO NOT STORE IT IN THE FREEZER.

2. Remember to take the safety syringe out of the refrigerator and allow it to reach room temperature before preparing it for injection (about 20 minutes).
3. Do not use the safety syringe after the expiration date shown on the outer box or syringe label. If it has expired, return the entire pack to the pharmacy.

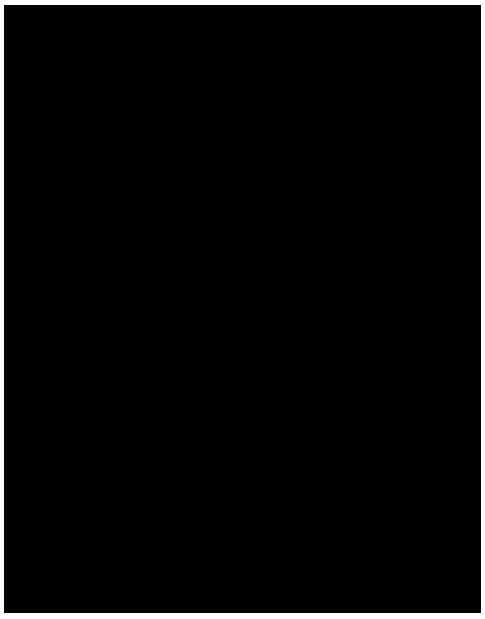
The injection site

The injection site is the place on the body where you are going to use the safety syringe. ACZ885 can be injected in either the upper outer thigh, abdomen or the upper outer arm. If you need more than one injection at a time, repeat the injection in the opposite thigh or arm.

Preparing the safety syringe ready for use

1. Take the box containing the safety syringe out of the refrigerator and leave it unopened for about 20 minutes so that it reaches room temperature.
2. When you are ready to use the safety syringe, wash your hands thoroughly with soap and water.
3. Clean the injection site.
4. Remove the safety syringe from the outer box and take it out of the plastic wrapper.
5. Inspect the safety syringe. DO NOT USE if it is broken or if the liquid has a distinctly brown discoloration or contains particles. In all these cases, return the entire product pack to the pharmacy.

How to use the safety syringe



Carefully remove the needle guard from the safety syringe. Discard the needle guard

Gently pinch the skin at the injection site and insert the needle.

[redacted]

[redacted]

Holding onto the finger flange, **slowly** depress the plunger as far as it will go. If some drug leaks from the injection site, insert the needle further.

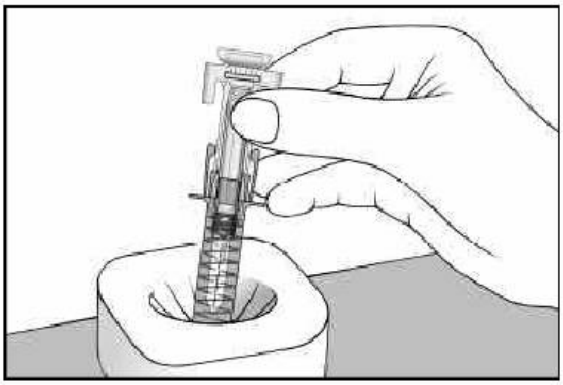
Keep the plunger pressed fully down while you hold the syringe in place for 5 seconds.

Keep the plunger fully depressed while you carefully lift the needle straight out from the injection site.

Slowly release the plunger and allow the syringe guard to automatically cover the exposed needle.

Disposal instructions

Dispose the used safety syringe immediately in a sharps container.



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