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Dose Finding, Safety and Efficacy of Monthly Subcutaneous Canakinumab Administration for the Treatment of Hyperglycemia in Metformin Monotherapy Treated Type 2 Diabetic Patients: a Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study

Authors:	Strange P, Chang I, Frusciante K

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List of abbreviations

ADCC	Antibody-dependent cell mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
b.i.d.	twice a day
CPO	Country Pharma Organization
CRD	Clinical Research and Development
CRO	Contract Research Organization
CSR	Clinical Study Report
ECG	Electrocardiogram
(e)CRF	Electronic Case Report/Record Form
FPG	fasting plasma glucose
GAD	Glutamic Acid Decarboxylase
hCG	human chorionic gonadotropin
hsCRP	high-sensitivity C-reactive protein
HEENT	Head, Eyes, Ears, Nose, Throat
HOMA	Homeostatic Model Assessment
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMS	Integrated Medical Safety
IRB	Institutional Review Board
IU	International Units
i.v.	intravenous(ly)
IVRS	Interactive Voice Response System
NGSP	National Glycohemoglobin Standardization Program
OGTT	Oral Glucose Tolerance Test
PPD	Purified protein derivative
PPG	post prandial glucose
REB	Research Ethics Board
SAE	serious adverse event
SMFG	Self-monitored fasting glucose
SUSARs	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TSH	Thyroid Stimulating Hormone
ULN	upper limit of normal
WFI	Water for injection

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
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.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs

Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Protocol synopsis:

Title of study: Dose Finding, Safety and Efficacy of Monthly Subcutaneous Canakinumab Administration for the Treatment of Hyperglycemia in Metformin Monotherapy Treated Type 2 Diabetic Patients: a Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study

Purpose and rationale:

The purpose of this study is to determine the optimal dose of canakinumab when dosed once a month under the skin to improve blood sugar control in early stage patients with type 2 diabetes mellitus. The optimal dose will be determined based on the safety, tolerability and efficacy (effects on $HbA_{1c)}$ results of the four canakinumab doses compared with placebo. After the 4-month primary analysis is completed, the optimal dose will be selected and all patients treated with canakinumab will be transferred to that selected dose. The study will then be continued for up to four years to provide information about long term effects and safety. The study is necessary to determine the dose for a much larger registration study studying canakinumab's potential to delay the progression of diabetes. The continuation of the study at the selected dose provides long term safety data at the earliest possible time during the clinical development of canakinumab. This can minimize the number of people exposed to canakinumab while still studying the effects and potential side effects of the compound.

The study design contains four periods:

Period I: Run-In
Period II: 4-Month Dose-finding
Period III: Intermediate
Period IV: Long-term continuation.

The rationale of the study design elements will be discussed in that sequence.

The Run-In Period includes two subcutaneous, single-blinded injections of placebo (blinded only to the patient), which allows study patients to get used to this procedure. Furthermore, metformin as the background therapy is introduced to drug naïve patients and optimized for patients already on metformin. Each patient will be titrated to their individual maximum tolerated dose. This allows a uniform study group in terms of background therapy and stable glycemic control to be randomized to the canakinumab therapy or placebo. The introduction run-in period is standard in this type of study and is also recommended in the (FDA's Draft Guidance for Industry, 2008) for the development of diabetes drugs.

The 4-Month Dose Finding Period of the trial is a classical dose response study design. Previous studies in other indications as well as diabetes have shown canakinumab to be well tolerated at doses up to 600 mg i.v. and 2 x 150 mg s.c. or considerably higher than the maximal dose tested in the present study. It's half-life in the body is more than two weeks. In rare inflammatory syndromes of Il-1β overproduction, canakinumab with dosing intervals up to six months have proven adequate to prevent disease activity flares. These three findings combined indicate that monthly dosing will be adequate to maintain therapeutic doses in the tissues for at least a month. While it would be possible to develop canakinumab for weekly dosing the added convenience of monthly dosing makes that choice reasonable. The choice of a double-blind, randomized placebo-controlled design is standard and ensures minimal if not complete elimination of any bias in addressing the endpoints. General diabetes education of all patients in the study will ensure somewhat better glycemic control simply by participation in the study. The glycemic control upper limit of HbA1c= 11% at Screening in the drug naïve patients is chosen to ensure that the vast majority of these patients will get in reasonable glycemic control from metformin monotherapy during the run-in period. The glycemic control upper limit of HbA1c= 9% at Screening in patients already treated with metformin will ensure all patients are in reasonable control after dose optimization. The inclusion criterion of a morning fasting plasma glucose <180 mg/dl at Visit 3 (Month -1), further ensures that patients are reasonably controlled prior to randomization and minimizes the risk of requiring rescue during the 4-month dose finding period. The canakinumab dose range from 5-150 mg spanning a 30-fold difference is chosen based on all

data to have likelihood to show a dose response curve with at least two doses at near maximal effect on HbA1c. Patients will be randomized to one of the four canakinumab doses or to placebo at a ratio of 1:1:1:1:2. The somewhat larger placebo group maximizes statistical power and as such minimizes the total number of patients needed to be exposed to canakinumab.

During the Intermediate Period, patients will stay on their randomized treatment and have monthly visits, until the selected dose is available. This is necessary to ensure that there is no disruption in dosing or safety monitoring while the 4-month dose finding period is completed and the selected dose is determined.

The Long-Term Continuation Period (after the selection of the optimal dose) provides an opportunity to obtain long-term data in parallel with conducting the phase 3 registration trials. This will ensure knowledge of long-term effects and side effects earlier in the drug development program and a more comprehensive data package available for Health Authority review. It therefore may represent a more efficient and safer way of developing drugs. The continuation of the placebo group is essential for appropriate evaluation of relatively rare side effects such as infections. To ensure appropriate glycemic control of study participants during the long follow-up period, rigorous criteria will precipitate add-on therapy with insulin glargine for all patients irrespective of treatment assignment. Insulin glargine is chosen because it is effective and in contrast to the other options of sulfonylureas, thiazolidinediones or dipeptidyl peptidase 4 inhibitors carries minimal risk of any interaction with the effects of the test drug canakinumab on the pancreatic β-cells. The combination of metformin and insulin glargine has proven very effective in clinical trials to date and additional therapy with a rapid acting insulin analog should only be necessary in limited cases.

Primary Objectives:

For Period II

- To assess safety and tolerability of four doses of ACZ885 (5 mg, 15 mg, 50 mg, and 150 mg) vs. placebo as an add-on regimen over 4 months in patients with T2DM pre-treated and continuing on a stable dose of metformin ≥ 1000 mg daily (or lower dose if required by local regulations).
- To assess the effect on HbA_{1c} of four doses of ACZ885 (5 mg, 15 mg, 50 mg, and 150 mg) vs. placebo as an add-on regimen over 4 months in patients with T2DM pre-treated and continuing on a stable dose of metformin ≥ 1000 mg daily (or lower dose if required by local regulations).

For Period IV

- To assess the safety and tolerability of active treatment of ACZ885, at the dose selected based on the efficacy and safety data from the 4-month treatment period vs. placebo, as an add-on regimen over a minimum of 24 months period in patients with T2DM pre-treated and continuing on a stable dose of metformin ≥ 1000 mg daily (or lower dose if required by local regulations).

Secondary Objectives:

For Period II

- To evaluate the effect of 4-month treatment of ACZ885 at doses 5 mg, 15 mg, 50 mg, and 150 mg vs. placebo on the following variables:
    - Area under the curve (AUC) and peak values of C-peptide following meal test
    - Area under the curve (AUC), 2-hour value and peak value of glucose and insulin following meal test
    - Insulin secretion rate derived based on glucose and C-peptide following meal test
    - Average and peak values based on 7-point glucose meter data
    - Fasting plasma glucose (FPG), insulin, HOMA2 B, HOMA2 IR, and QUICKI index
    - hsCRP
    - Pharmacokinetics covariate analysis utilizing population PK approach

- Summarize proportions of cardiovascular events and infections.

For Period IV

- To evaluate the effect of long-term treatment of ACZ885 at the dose selected based on the efficacy and safety data from the 4-month treatment period vs. placebo on the following variables:
  - Duration of insulin use and insulin dose
  - Area under the curve (AUC) and peak values of C-peptide following meal test
  - Area under the curve (AUC), 2-hour value and peak value of glucose and insulin following meal test
  - Insulin secretion rate derived based on glucose and C-peptide following meal test
  - HbA1c , Fasting plasma glucose (FPG), insulin, HOMA2 B, HOMA2 IR, and QUICKI index
  - Summarize incidence of cardiovascular events and infections.

Population:

The study population will consist of a representative group of male and female patients (18-74 years of age, inclusive) with type 2 diabetes mellitus either naïve to chronic pharmacological diabetes therapy, or currently in stable treatment with metformin monotherapy as their first chronic glucose lowering therapy. It is expected that about 1100 patients need to be screened at approximately 100 centers worldwide to recruit enough patients into the run-in period to achieve the actual target of at least 600 patients evaluable for the 4-month primary analysis. In order to achieve the target of 600 evaluable patients (an evaluable patient has at least one post randomization HbA_{1c} value) additional patients may be recruited and randomized. Efforts should be exercised that no single site randomizes less than six patients.

Inclusion criteria:

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

1. Patients must give written informed consent before any study related procedures are performed.
2. Patients must have a documented diagnosis of Type 2 diabetes confirmed by WHO criteria either a FPG≥ 7.0 mmol/l (126 mg/dl) or an OGTT test 2-hour PG ≥ 11.1 mmol/l (200 mg/dl).
3. Patients must:
   - be naïve to anti-diabetes drug therapy (except for short term treatment courses with insulin in connection with hospitalization, etc.)
   - have an HbA_{1c} between 7.5% and 11% (inclusive) at Screening analyzed by the Central Laboratory
   - be eligible for metformin monotherapy

   OR
   - be on stable metformin monotherapy treatment for at least three months at Screening
   - have an HbA_{1c} between 7.0% and 9% (inclusive) at Screening analyzed by the Central Laboratory
   - take metformin as their first and only treatment with anti-diabetes drug therapy (except for short term treatment courses with insulin in connection with hospitalization, etc.)
4. Patients must have a morning fasting plasma glucose result < 180 mg/dl at Visit 3 (Month -1) analyzed by the Central Laboratory.
5. At the Randomization Visit (Month 0), patients must be on a daily dose of metformin ≥ 1000 mg (or less if local regulation does not permit 1000 mg/day).
6. Age from 18-74 years, inclusive, and of either sex.

Exclusion criteria

Patients will be excluded if they fulfill any of the following criteria at Screening or prior to Randomization (Month 0):

1. Any of the following significant laboratory abnormalities:
    - Serum GAD-antibody positivity analyzed by the Central Laboratory.
    - Clinically significant TSH outside of normal range at Screening analyzed by the Central Laboratory.
    - Renal function indicating high risk metformin use, including serum creatinine concentrations (≥1.5 mg/dL for males, ≥1.4 mg/dL for females) or other evidence of abnormal creatinine clearance.
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 x upper limit of normal (ULN) at Screening, confirmed with repeat measure within one week.
2. History or current findings of active pulmonary disease (e.g. tuberculosis, fungal diseases) as evidenced by any of the following:
    - History of positive PPD skin test result with positive chest x-ray and no completion of treatment
    - A positive PPD skin test plus a positive chest x-ray during the screening period.
    - Requirement for administration of antibiotics against latent tuberculosis (e.g., isoniazide). Courses of antibiotic therapy started prior to entering the study should not be prematurely terminated to allow inclusion into the study.
3. Known presence or suspicion of active or recurrent bacterial, fungal or viral infection at the time of enrollment, including patients with evidence of Human Immunodeficiency Virus (HIV) infection, Hepatitis B and Hepatitis C infections (based on history and/or findings from the Central Lab).
4. Any surgical or underlying hepatic, hematologic, pulmonary, infectious, autoimmune or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in immunodulatory therapy.
5. Any systemic treatment or local treatment of any immune modulating agent in doses with systemic effects.
6. Stroke, myocardial infarction, acute coronary syndrome, revascularization procedure or recurrent TIA within the last 6 months.
7. Unwillingness to use insulin glargine as the additional medication should glycemic control deteriorate.
8. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
9. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).

For a complete list of all exclusion criteria, see Section 5.2. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

Investigational and reference therapy:

Initially patients will be assigned to one of the following treatment arms in a 2:1:1:1:1 ratio:

- Placebo
- canakinumab 5 mg
- canakinumab 15 mg
- canakinumab 50 mg
- canakinumab 150 mg

In Period IV Long-term continuation, three canakinumab doses will be removed after the 4-month dose-finding analysis and all patients randomized to one of the canakinumab arms will be switched to the selected canakinumab dose. Placebo patients will remain on placebo.

Study Design

This study consists of four periods: screening (Period I), dose-finding (Period II), intermediate (Period III), and long-term continuation (Period IV). A parallel-group, randomized, double-blind, placebo-controlled design is used. Upon completion of Period II for all randomized patients, the primary analysis will take place for the purpose of dose selection. A futility analysis may be conducted when 300 patients complete Period II. However, if by the time 300 patients complete Period II, all patients are already enrolled, the futility analysis may not take place. No other interim analysis is planned.

Period I:

After an up to three week screening period eligible patients will start a two month run-in placebo period. Metformin will be initiated in diabetes drug naïve patients and optimized to maximal tolerated dose in patients already treated with metformin.

Period II:

Eligible patients are randomized to one of four canakinumab doses or placebo in a 1:1:1:1:2 ratio for the four-month treatment during the dose finding period. During this period patients will visit the clinic monthly and have their medication delivered in the clinic at each visit. During this period, patients with consecutive morning fasting glucose >200 mg/dl will be treated with a daily injection of insulin glargine as add-on therapy.

Period III:

After the patient completes the 4-month Visit, the intermediate period begins. Patients will continue their randomized treatment and have brief visits to the clinic every month. From this point forward patients with consecutive HbA_{1c} >7.5% will be treated with a daily injection of insulin glargine as add-on therapy. All patients will stay in this period until the primary analysis is completed and the optimal dose is selected.

Period IV:

After the optimal dose is selected, patients will begin Period IV at their next scheduled monthly visit. From that point, the patient will continue to come to the clinic for monthly study drug injections but have all other study assessments done quarterly. Patients previously randomized to one of the four canakinumab doses will be switched onto the selected dose. The placebo group will remain on placebo. Period IV will continue for a minimum of 24 months (maximum of 42 months), based on Sponsor approval.

Efficacy Assessments:

- HbA_{1c} measured by NGSP certified methodology
- FPG
- Fasting Insulin
- Mixed Liquid Meal Test

- Fasting Lipids

Other Assessments:

- Physical Exam
- Labs
- ECG
- PK/PD
- Weight
- Vitals
- Pharmacogenetic, pharmacogenomic and soluble biomarker analyses

Data Analysis:

Efficacy

The primary efficacy variable for the dose finding period (Period II) is the change from baseline in HbA_{1c} at Month 4. An analysis of covariance (ANCOVA) followed by two-sided Dunnett's test for multiple comparisons with a control will be used for the comparison of each active dose versus placebo. The ANCOVA model will include treatment and meformin dose category (<1500mg and ≥ 1500mg daily) as the classification variables and baseline as the covariate. Nominal 95% confidence interval for the estimated difference between each active dose and placebo will also be determined based on the ANCOVA model.

Secondary efficacy variables including fasting plasma glucose (FPG), insulin, hsCRP (in log scale), fasting lipids, and AUCs of postprandial glucose, insulin, and C-peptide will be analyzed similarly using ANCOVA model. The change from baseline in hsCRP (in log scale) will be analyzed using ANCOVA model.

Efficacy data collected during the transition period (Period III), including insulin use, will be summarized by dose group and by monthly interval since Month 4.

The duration of rescue insulin use in Period IV, as a ratio to Period IV treatment duration, will be compared between the active and placebo treatment groups using nonparametric approach. Similarly, the insulin dose at Month 6, 12, 18, and 24 will be compared between the active and placebo treatment groups. Other efficacy data collected during Period IV will be compared between the active and placebo treatment using ANCOVA as appropriate.

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. In addition, the incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term. SAEs, if any, will be narrated.

Adverse events related to major cardiovascular events (MACE), serious infections and hypoglycemia will be specifically investigated. The incidence of hypoglycemia will be tabulated separately for patients with or without rescue insulin treatment and analyzed using Poisson regression.

Laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), summary statistics of raw data and change from baseline (mean, medians, standard deviations, ranges) and by flagging of notable values in data listings.

Sample Size Calculation

The primary objective of the study, dose finding, will be based on change from baseline in HbA_{1c} at Month 4. Comparison of each dose versus placebo will be performed using analysis of covariance followed by Dunnett's multiple comparison procedure. The study at a sample size of N=100 for each dose group and N=200 for the placebo group will have an ≥80% power to demonstrate at least one active dose is significantly different from placebo, i.e. rejecting at least one of the hypotheses H_{01}, H_{02},

H_{03}, and $H_{04,}$ when one or more of the active doses truly differ from placebo in HbA_{1c} by 0.41 at an overall α level of 0.05 (two-sided) with Dunnett's test. The assumed population standard deviation is 1 for the sample size calculation.

1 Background

The type 2 diabetes mellitus worldwide incidence and prevalence increase rapidly and are projected to continue this trajectory for at least the next 40 years. Current therapies for treating type 2 diabetes are focused on managing hyperglycemia and with the possible exceptions of the thiazolidinediones and exenatide have no or little effect on preventing the inexorable decline of pancreatic β-cell function. Consequently, the vast majority of type 2 diabetes patients progress to insulin therapy with the current median time from diagnosis of about eight years in the developed economies. While insulin therapy works well it is associated with the acute complication of life threatening hypoglycemia and can therefore be difficult to use to achieve adequate glycemic control. The poor glycemic control associated with the disease progression leads to the complications of retinopathy, nephropathy and neuropathy.

Pre-clinical data suggests Il-1β is of key importance in the progressive functional impairment and destruction of β-cells in type 2 diabetes. Blocking Il-1β activity with an Il-1 receptor antagonist as well as a neutralizing Il-1β antibody in clinical trials reduced HbA_{1c} even in the short term of 4 months (Larsen, et al. 2007). Neutralization of Il-1β activity in the pancreatic islets is thus emerging as an attractive target for the treatment of type 2 diabetes. The anticipated effect of such intervention is a short term amelioration of the negative impact Il-1β has on β-cell function resulting in some restoration of first phase insulin response that is among the earliest deficits in the natural history of normal function through impaired glucose tolerance to type 2 diabetes (Gerich. 2003). That improvement leads to the demonstrated glycemic control benefit through rapid suppression of hepatic glucose production and consequent diminished need for second phase insulin release. Longer term the effects of diminished Il-1β induced β-cell apoptosis is expected to lead to preserved β-cell function and therefore clinical arrest of disease progression.

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. This results in neutralized bioactivity of IL-1β but does not prevent the binding of the natural inhibitor, IL-1Ra, nor binding to IL-1α. As an IgG1 antibody, there is a potential for canakinumab to mediate complement fixation and antibody-dependent cell mediated cytotoxicity (ADCC). However, inasmuch as the interaction between IL-1β and canakinumab is unlikely to be cell-associated, such a mechanism is not likely to occur.

Preliminary results show that canakinumab treatment of adult patients with Muckle-Wells syndrome (MWS) cause rapid and complete clinical and laboratory remission in all patients (Lachmann et al 2006, Lachmann et al 2008). It is noteworthy that canakinumab has a long half life duration ($t_{1/2}$ = 21-28 days) and may have the advantage of an infrequent dosing schedule (i.e. anakinra $t_{1/2}$ = 6 hours and should be administered daily (So, et al 2007), thus, improving patient convenience.

As of December 10th, 2007 a total of 420 patients including 26 children aged ≥ 4 years have received canakinumab in clinical trials across many disease states including Muckle Wells Syndrome, systemic Juvenile Idiopathic Arthritis (sJIA) and adult and Juvenile Rheumatoid

Arthritis (RA, JRA). The safety, tolerability and efficacy data of canakinumab in completed studies and studies with an interim analysis, are available from 137 male or female patients, including 3 children. The doses administered i.v. ranged from 0.3 mg/kg to 10 mg/kg or a fixed dose of 600 mg, and from 0.5 mg/kg to 2 mg/kg s.c. or fixed doses of 150 and 300 mg s.c. The frequency of dosing ranged from single dose to weekly repeated administration. So far the maximum duration of exposure to canakinumab is 2 1/2 years for the first patients enrolled.

As described in the [Investigators' Brochure], ACZ885 canakinumab displayed typical pharmacokinetics of an IgG1-type antibody. Comparison of AUC and peak concentration across dose groups indicates that within the dose range the pharmacokinetics was dose proportional. There was no indication of accelerated clearance (antibody formation) from the terminal phases of the concentration-vs.-time profiles. Detailed background information on the chemistry, pharmacology, toxicology, preclinical and clinical data of canakinumab is also given in the [Investigators' Brochure].

Canakinumab has generally been well tolerated. Treatment discontinuations were rare (3 out of 137 patients receiving canakinumab) and not suspected to have a relationship with the study drug. Among the 554 patients enrolled, as of 10 December 2007, 27 SAEs were reported (10 in canakinumab treated, 13 in canakinumab or placebo treated, code not broken, and 4 in placebo or active control treated patients). In seven of the 27 SAEs the investigator suspected a relationship between the event and the study medication. Six SAEs were infections, including four respiratory tract infections, one erysipelas and one urosepsis. Three of the infectious adverse events were suspected to have relationship with the study drug. All infections responded to antibiotics treatment. For more details, please refer to the latest available edition of the Investigators' Brochure.

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. Preserving pancreatic β-cells has in type 1 diabetes been shown to be associated with lower risk of both acute and chronic complications, which is expected to occur in type 2 diabetes as well.

In summary there is thus compelling evidence to test the efficacy as well as finding an optimal dose for clinical development of the Il-1β neutralizing antibody canakinumab.

2 Purpose and rationale

The purpose of this study is to determine the optimal dose of canakinumab when dosed once a month under the skin to improve blood sugar control in early stage patients with type 2 diabetes mellitus. The optimal dose will be determined based on the safety, tolerability and efficacy (effects on $HbA_{1c)}$ results of the four canakinumab doses compared with placebo. After the 4-month primary analysis is completed, the optimal dose will be selected and all patients treated with canakinumab will be transferred to that selected dose. The study will then be continued for up to four years to provide information about long term effects and safety. The study is necessary to determine the dose for a much larger registration study studying canakinumab's potential to delay the progression of diabetes. The continuation of the study at the selected dose provides long term safety data at the earliest possible time during

the clinical development of canakinumab. This can minimize the number of people exposed to canakinumab while still studying the effects and potential side effects of the compound.

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The 4-Month Dose Finding Period of the trial is a classical dose response study design. Previous studies in other indications as well as diabetes have shown canakinumab to be well tolerated at doses up to 600 mg i.v. and 2 x 150 mg s.c. or considerably higher than the maximal dose tested in the present study. It's half-life in the body is more than two weeks. In rare inflammatory syndromes of Il-1β overproduction, canakinumab with dosing intervals up to six months have proven adequate to prevent disease activity flares. These three findings combined indicate that monthly dosing will be adequate to maintain therapeutic doses in the tissues for at least a month. While it would be possible to develop canakinumab for weekly dosing the added convenience of monthly dosing makes that choice reasonable. The choice of a double-blind, randomized placebo-controlled design is standard and ensures minimal if not complete elimination of any bias in addressing the endpoints. General diabetes education of all patients in the study will ensure somewhat better glycemic control simply by participation in the study. The glycemic control upper limit of HbA_{1c}= 11% at Screening in the drug naïve patients is chosen to ensure that the vast majority of these patients will get in reasonable glycemic control from metformin monotherapy during the run-in period. The glycemic control upper limit of HbA_{1c}= 9% at Screening in patients already treated with metformin will ensure all patients are in reasonable control after dose optimization. The inclusion criterion of a morning fasting plasma glucose <180 mg/dl at Visit 3 (Month -1), further ensures that patients are reasonably controlled prior to randomization and minimizes the risk of requiring rescue during the 4-month dose finding period. The canakinumab dose range from 5-150 mg spanning a 30-fold difference is chosen based on all data to have likelihood to show a dose response curve with at least two doses at near maximal effect on HbA_{1c}. Patients will be randomized to one of the four canakinumab doses or to placebo at a ratio of 1:1:1:1:2. The somewhat larger placebo group maximizes statistical power and as such minimizes the total number of patients needed to be exposed to canakinumab.

During the Intermediate Period, patients will stay on their randomized treatment and have monthly visits, until the selected dose is available. This is necessary to ensure that there is no

disruption in dosing or safety monitoring while the 4-month dose finding period is completed and the selected dose is determined.

The Long-Term Continuation Period (after the selection of the optimal dose) provides an opportunity to obtain long-term data in parallel with conducting the phase 3 registration trials. This will ensure knowledge of long-term effects and side effects earlier in the drug development program and a more comprehensive data package available for Health Authority review. It therefore may represent a more efficient and safer way of developing drugs. The continuation of the placebo group is essential for appropriate evaluation of relatively rare side effects such as infections. To ensure appropriate glycemic control of study participants during the long follow-up period, rigorous criteria will precipitate add-on therapy with insulin glargine for all patients irrespective of treatment assignment. Insulin glargine is chosen because it is effective and in contrast to the other options of sulfonylureas, thiazolidinediones or dipeptidyl peptidase 4 inhibitors carries minimal risk of any interaction with the effects of the test drug canakinumab on the pancreatic β-cells. The combination of metformin and insulin glargine has proven very effective in clinical trials to date and additional therapy with a rapid acting insulin analog should only be necessary in limited cases daily (Yki-Jarvinen, et al 2006).

3 Objectives

3.1 Primary objectives

For Period II

- To assess safety and tolerability of four doses of ACZ885 (5 mg, 15 mg, 50 mg, and 150 mg) vs. placebo as an add-on regimen over 4 months in patients with T2DM pre-treated and continuing on a stable dose of metformin ≥ 1000 mg daily (or lower dose if required by local regulations).
- To assess the effect on HbA1c of four doses of ACZ885 (5 mg, 15 mg, 50 mg, and 150 mg) vs. placebo as an add-on regimen over 4 months in patients with T2DM pre-treated and continuing on a stable dose of metformin ≥ 1000 mg daily (or lower dose if required by local regulations).

For Period IV

- To assess the safety and tolerability of active treatment of ACZ885, at the dose selected based on the efficacy and safety data from the 4-month treatment period vs. placebo, as an add-on regimen over a minimum of 24 months period in patients with T2DM pre-treated and continuing on a stable dose of metformin ≥ 1000 mg daily (or lower dose if required by local regulations).

3.2 Secondary objectives

For Period II:

- To evaluate the effect of 4-month treatment of ACZ885 at doses 5 mg, 15 mg, 50 mg, and 150 mg vs. placebo on the following variables:

- Area under the curve (AUC) and peak values of C-peptide following meal test
- Area under the curve (AUC), 2-hour value and peak value of glucose and insulin following meal test
- Insulin secretion rate derived based on glucose and C-peptide following meal test
- Average and peak values based on 7-point glucose meter data
- Fasting plasma glucose (FPG), insulin, HOMA2 B, HOMA2 IR, and QUICKI index
- hsCRP
- Pharmacokinetics covariate analysis utilizing population PK approach

- Summarize proportions of cardiovascular events and infections.

For Period IV:

- To evaluate the effect of long-term treatment of ACZ885 at the dose selected based on the efficacy and safety data from the 4-month treatment period vs. placebo on the following variables:
  - Duration of insulin use and insulin dose
  - Area under the curve (AUC) and peak values of C-peptide following meal test
  - Area under the curve (AUC), 2-hour value and peak value of glucose and insulin following meal test
  - Insulin secretion rate derived based on glucose and C-peptide following meal test
  - HbA_{1c}, Fasting plasma glucose (FPG), insulin, HOMA2 B, HOMA2 IR, and QUICKI index
- Summarize incidence of cardiovascular events and infections.

3.3 Exploratory objectives

- To explore the effect of 4-month treatment of ACZ885 at doses 5 mg, 15 mg, 50 mg, and 150 mg vs. placebo on the following variables:
  - Circulating inflammatory markers.
  - Fasting lipids
  - Pharmacogenetic signatures.
  - Pharmacogenomics including mRNA expression profiles in peripheral blood.
- To explore the effect of canakinumab at different doses and relative to placebo on health-related outcomes as measured by the Patient Utility Index derived from patients responses on the EQ-5D at Visit 8 (Month 4) and at timepoints every 3 months thereafter.

4 Study design

This study consists of four periods: screening (Period I), dose-finding (Period II), intermediate (Period III), and long-term continuation (Period IV). A parallel-group, randomized, double-blind, placebo-controlled design is used. Upon completion of Period II for all randomized patients, the primary analysis will take place for the purpose of dose selection. A futility

analysis may be conducted when 300 patients complete Period II. However, if by the time 300 patients complete Period II, all patients are already enrolled, the futility analysis may not take place. No other interim analysis is planned. No other interim analysis is planned.

Period I:

After an up to three week screening period eligible patients will start a two month run-in placebo period. Metformin will be initiated in diabetes drug naïve patients and optimized to maximal tolerated dose in patients already treated with metformin.

Period II:

Eligible patients are randomized to one of four canakinumab doses or placebo in a 1:1:1:1:2 ratio for the four-month treatment during the dose finding period. During this period patients will visit the clinic monthly and have their medication delivered in the clinic at each visit. During this period, patients with consecutive morning fasting glucose >200 mg/dl will be treated with a daily injection of insulin glargine as add-on therapy.

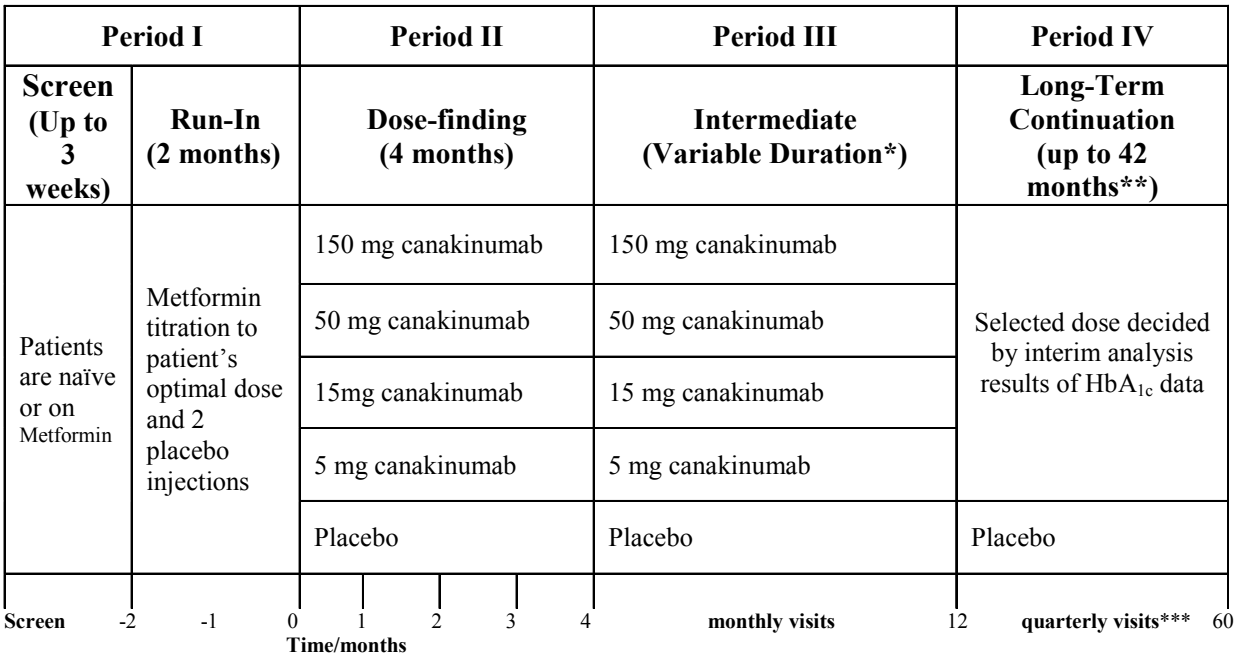
Period III:

After the patient completes the 4-month Visit, the intermediate period begins. Patients will continue their randomized treatment and have brief visits to the clinic every month. From this point forward patients with consecutive HbA_{1c} >7.5% will be treated with a daily injection of insulin glargine as add-on therapy. All patients will stay in this period until the primary analysis is completed and the optimal dose is selected.

Period IV:

After the optimal dose is selected, patients will begin Period IV at their next scheduled monthly visit. From that point, the patient will continue to come to the clinic for monthly study drug injections but have all other study assessments done quarterly. Patients previously randomized to one of the four canakinumab doses will be switched onto the selected dose. The placebo group will remain on placebo. Period IV will continue for a minimum of 24 months (maximum of 42 months), based on Sponsor approval.

Figure 4-1 Study Design



*The duration of this period will be dependent on how long it takes for 600 patients to complete the 4-month dose-finding period and the additional time it takes for the results of the dose selection to become available. Each patient may spend a different length of time in this period but will follow the same visit schedule. When the selected dose is determined, all patients will enter Period IV at their next monthly visit.

**Patients will remain in the long-term continuation period for a minimum of 24 months (up to 42 months).

***Patients will return to the clinic for monthly injections but will have other study assessments done quarterly.

5 Population

The study population will consist of a representative group of male and female patients (18-74 years of age, inclusive) with type 2 diabetes mellitus either naïve to chronic pharmacological diabetes therapy, or currently in stable treatment with metformin monotherapy as their first chronic glucose lowering therapy. It is expected that about 1100 patients need to be screened at approximately 100 centers worldwide to recruit enough patients into the run-in period to achieve the actual target of at least 600 patients evaluable for the 4-month primary analysis. In order to achieve the target of 600 evaluable patients (an evaluable patient has at least one post randomization HbA_{1c} value) additional patients may be recruited and randomized. Efforts should be exercised that no single site randomizes less than six patients.

5.1 Inclusion criteria

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

1. Patients must give written informed consent before any study related procedures are performed.

2. Patients must have a documented diagnosis of Type 2 diabetes confirmed by WHO criteria either a FPG≥ 7.0 mmol/l (126 mg/dl) or an OGTT test 2-hour PG ≥ 11.1 mmol/l (200 mg/dl).
3. Patients must:
    - be naïve to anti-diabetes drug therapy (except for short term treatment courses with insulin in connection with hospitalization, etc.)
    - have an HbA_{1c} between 7.5% and 11% (inclusive) at Screening analyzed by the Central Laboratory
    - be eligible for metformin monotherapy

    OR
    - be on stable metformin monotherapy treatment for at least three months at Screening
    - have an HbA_{1c} between 7.0% and 9% (inclusive) at Screening analyzed by the Central Laboratory
    - take metformin as their first and only treatment with anti-diabetes drug therapy (except for short term treatment courses with insulin in connection with hospitalization, etc.)
4. Patients must have a morning fasting plasma glucose result < 180 mg/dl at Visit 3 (Month -1) analyzed by the Central Laboratory.
5. At the Randomization Visit (Month 0), patients must be on a daily dose of metformin ≥ 1000 mg (or less if local regulation does not permit 1000 mg/day).
6. Age from 18-74 years, inclusive, and of either sex.

5.2 Exclusion criteria

Patients will be excluded if they fulfill any of the following criteria at Screening or prior to Randomization (Month 0):

1. Any of the following significant laboratory abnormalities:
    - Serum GAD-antibody positivity analyzed by the Central Laboratory.
    - Clinically significant TSH outside of normal range at Screening analyzed by the Central Laboratory.
    - Renal function indicating high risk metformin use, including serum creatinine concentrations (≥1.5 mg/dL for males, ≥1.4 mg/dL for females) or other evidence of abnormal creatinine clearance.
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2 x upper limit of normal (ULN) at Screening, confirmed with repeat measure within one week.
2. History or current findings of active pulmonary disease (e.g. tuberculosis, fungal diseases) as evidenced by any of the following:
    - History of positive PPD skin test result with positive chest x-ray and no completion of treatment
    - A positive PPD skin test plus a positive chest x-ray during the screening period.

- Requirement for administration of antibiotics against latent tuberculosis (e.g., isoniazide). Courses of antibiotic therapy started prior to entering the study should not be prematurely terminated to allow inclusion into the study.

3. One of the risk factors for TB such as:
   - History of any of the following: residence in a congregate setting (e.g. jail or prison, homeless shelter, or chronic care facility), substance abuse (e.g. injection or non-injection); health-care workers with unprotected exposure to patients who are at high risk of TB or patients with TB disease before the identification and correct airborne precautions of the patient, or
   - Close contact (i.e. share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours)) with a person with active pulmonary TB disease.
4. Known presence or suspicion of active or recurrent bacterial, fungal or viral infection at the time of enrollment, including patients with evidence of Human Immunodeficiency Virus (HIV) infection, Hepatitis B and Hepatitis C infections (based on history and/or findings from the Central Lab).
5. Any surgical or underlying hepatic, hematologic, pulmonary, infectious, autoimmune or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in immunodulatory therapy.
6. Any systemic treatment or local treatment of any immune modulating agent in doses with systemic effects.
7. No live vaccinations within 3 months prior to the Randomization Visit or live vaccinations planned during the trial and up to three months following the last dose.
8. Stroke, myocardial infarction, acute coronary syndrome, revascularization procedure or recurrent TIA within the last 6 months.
9. Unwillingness to use insulin glargine as the additional medication should glycemic control deteriorate.
10. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
11. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
12. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
13. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant. UNLESS they are
    - women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner

- women whose partners have been sterilized by vasectomy or other means
- using a highly effective method of birth control (i.e. one that results in a less than 1% per year failure rate when used consistently and correctly, such as implants, injectables, combined oral contraceptives, and some intrauterine devices (IUDs), Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) are not acceptable

Reliable contraception should be maintained throughout the study and for 90 days after study drug discontinuation.

Woman are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL [***for US only:*** and estradiol < 20 pg/mL] or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

15. Inability or unwillingness to comply with study procedures as evidence with compliance during screening and the run-in period.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

6 Treatment

6.1 Investigational and control drugs

To minimize potential bias due to confounding factors and to accurately assess the effect of canakinumab doses, placebo is chosen as a comparator. Monthly dosing is feasible based on canakinumab's plasma half life of 2 to 3 weeks and its ability to prevent relapses for up to six months in Il-1β mediated autoinflammatory syndromes (i.e., Muckle-Wells Syndrome). The highest dose in the present study of 150 mg is expected to provide neutralization in plasma of Il-1β effect for at least one month. Based on existing study data the optimal dose is expected to be around 50 mg, but due to uncertainty about the lower end of the dose response relation the lowest dose tested of 5 mg is 10 times lower than the anticipated response.

Novartis will supply canakinumab [labeled as ACZ885] and its placebo dummy in individual 6 mL glass vials each containing 25 mg canakinumab or 150 mg canakinumab or placebo powder as a lyophilized cake. Study drug will be supplied as open label medication to the site. An unblinded designee at the site will reconstitute the appropriate dose and give it to the blinded site personnel or patient to inject in order to maintain the blind. Instructions for reconstituting and dispensing the study drug will be included in the Pharmacist Instruction Manual.

Table 6-1 Open Label Study Drug

Open-label dose strength supplied to site (lyophilized cake)	25 mg	150mg	placebo*
Dose of injection made from lyophized cake	15 mg 5 mg	150 mg 50 mg	placebo
* Placebo lyophilized cake will be reconstituted and then used to dilute the 25mg or 150mg solutions to make 5mg, 15mg and 50mg injections.			

6.2 Treatment arms

At randomization, patients will be assigned to one of the following treatment arms in a 2:1:1:1:1 ratio:

- Placebo
- canakinumab 5 mg
- canakinumab 15 mg
- canakinumab 50 mg
- canakinumab 150 mg

In Period IV Long-term continuation, three canakinumab doses will be removed after the 4-month dose-finding analysis and all patients randomized to one of the canakinumab arms will be switched to that selected canakinumab dose. Placebo patients will remain on placebo.

6.3 Treatment assignment

At randomization (Month 0/Visit 4), the investigator will confirm whether the patient fulfils all the inclusion/exclusion criteria. If so, then the investigator will instruct the independent, unblinded pharmacist/ nurse/ physician to call the Interactive Voice Response System (IVRS) to randomize the patient and obtain the assigned treatment arm. All eligible patients will be given a randomization number from IVRS that assigns them to one of the treatment arms. The randomization number will not be communicated to the caller.

To ensure that treatment assignment is unbiased and concealed from patients and investigator staff the randomization numbers will be generated using the following procedure: A patient randomization list will be produced by the IVRS 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.

The randomization scheme for patients will be reviewed and approved by a member of the Novartis Biostatistics Quality Assurance Group.

Randomization will be stratified by previous chronic diabetes medication (naïve or previously treated with metformin) and by country.

6.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysis will remain blind to the identity of the treatment from the time of randomization until the 4-month database lock using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone involved in the study except for the unblinded person at the site who is responsible for preparing the study medication (2) The identity of the canakinumab/placebo treatments will be concealed to the patient by the use of study drugs in form of syringes filled with reconstituted canakinumab solutions that are all identical in appearance. Only the actual canakinumab (or placebo) vials with lyophilisate will be supplied "open-label". (3) An independent, unblinded qualified study person (e.g. pharmacist, physician or nurse) will call the IVRS provider to randomize and receive the treatment assignment information. He/she will then prepare the appropriate study drug. This person will not perform any other study assessments.

This independent, unblinded pharmacist/nurse/physician(s) will make sure that no other person (other than the unblinded monitor) will have access to the medication and drug administration documentation.

During the entire study (Periods I-IV), patients, site personnel, sponsor staff with direct contact with sites and the adjudication committee will remain blinded to the identity of the treatment assignments and the results of the primary analysis until the database is locked for Period IV. Unblinded Novartis personnel without direct contact with sites will be responsible for the primary analysis procedures.

Upon completion of the randomization call, the IVRS provider will automatically forward a **blinded** Randomization Confirmation Report to the investigator.

Unblinding will only occur in the case of patient emergencies (see Section 6.5.9), at the time of the 4-month dose-finding analysis and at the conclusion of the study.

6.5 Treating the patient

6.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). Only the assigned patient number should be entered in the field labeled "Patient ID" on the eCRF data entry screen (e.g. enter '1', '2', etc.). Once assigned to a patient, a patient number will not be reused. If the patient fails to be randomized for any reason, the reason for not being randomized will be entered on the Screening Log, and the Demography CRF should also be completed.

6.5.2 Dispensing the study drug

An independent, unblinded pharmacist/nurse/physician will select the study drug packages to be used for drug administration to the patient after calling the IVRS and obtaining the

treatment assignment information at randomization. The unblinded pharmacist/nurse/ physician may call back into IVRS to review the treatment assignment of a patient at anytime. Immediately before preparing the drugs for administration to the patient, the unblinded pharmacist/nurse/physician will document which drug has been prepared in the source documents, Pharmacist Log, Drug Preparation Form for Unblinded Personnel, Pharmacist Drug Dispensing Form, containing that patient's unique patient number.

6.5.3 Study drug supply, storage and tracking

Study drug 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 designated study person has access. The person handling this drug shipment (if other than the unblinded designee) should have no responsibility for patient assessments as unblinding may occur based on what shipments are received. Upon receipt, all study drug should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

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

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

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

6.5.3.1 Storage of canakinumab/placebo vials

Canakinumab powder for solution for injection (active/placebo) must be stored in a locked refrigerator at 2-8°C and must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations.

6.5.4 Instructions for prescribing, preparing and taking the study drug

All eligible patients will receive placebo at Visit 2 and then switch to randomized drug (canakinumab or placebo) starting at Visit 4 (Month 0). Patients will receive one s.c. injection of canakinumab (or its matching placebo) monthly. Instructions for reconstituting and dispensing the study drug will be included in the Pharmacist Instruction Manual.

6.5.5 Permitted study drug dose adjustments and interruptions

Study drug dose adjustments and/or interruptions are not permitted.

6.5.6 Rescue medication

6.5.6.1 Period II (Months 0-4)

During Period II, consecutive fasting plasma glucose results greater than 200 mg/dl (failure criterion) drawn in the clinic and analyzed in the Central laboratory will prompt initiation of insulin glargine given once daily as described in section 6.5.6.3 starting at the next clinic visit.

Use of insulin glargine must be recorded after start of study drug in the (e)CRF.

6.5.6.2 Period III and IV

During Periods III and IV, consecutive HbA_{1c} results greater than 7.5% (failure criterion) will prompt initiation of insulin glargine given once daily as described in section 6.5.6.3 starting at the next clinic visit.

Should consecutive HbA_{1c} results greater than 7.5% (failure criterion) arise after more than six months of insulin glargine titration as described in section 6.5.6.3 the investigator may at her or his discretion add-on meal insulin, either a rapid acting insulin analogue or regular human insulin according to section 6.5.6.6.

Use of rescue medication must be recorded after start of study drug in the (e)CRF. Patients requiring rescue medication at anytime will be considered as treatment failures in the analysis of HbA_{1c} and other glycemic variables. The primary efficacy assessment for Period IV will be the incidence, duration, and dose of insulin use. See Section 10.4.3 for more details.

6.5.6.3 Insulin glargine (or insulin NPH, if insulin glargine is not available locally)

Initiation of insulin glargine can occur only when the criteria in either of the sections 6.5.6.1 or 6.5.6.2 are met.

Novartis will assure supply of insulin glargine commercial product through a prescription card or other local country practice for use in the study as open label medication, not labeled specifically for each patient. The lot number of each dispensed vial should be documented in the patient's source.

Insulin glargine is preferably dosed prior to breakfast, but can be dosed at any time of day according to the patient's and investigator's discretion as long at it is dosed at approximately the same time each day. The starting dose should be 10 IU.

6.5.6.4 Insulin glargine dose titration: target range and size of adjustments

The dose will be titrated based on self-monitored morning fasting glucose concentration (SMFG) with a plasma target range for the median of the trailing five values of 90-120 mg/dl (5.0-6.7 mmol/l) or blood target of 81-108 mg/dl (4.5-6.0 mmol/l), inclusive.

When the median of the trailing five plasma values is less than 90 mg/dl (5.0 mmol/l) or blood target 81 mg/dl (4.5 mmol/l) at the determined titration time, the insulin will be decreased by 10% or minimally 1U. It is thus technically feasible to titrate the insulin to discontinuation should the need for insulin diminish (e.g. from effects of the study drug).

When the median of the trailing five plasma values is above 120 mg/dl (6.7 mmol/l) or blood target 108 mg/dl (6.0 mmol/l) at the determined titration time, the insulin will be increased by 10% or minimally 2 IU.

6.5.6.5 Insulin glargine dose titration: adjustment frequency

Insulin glargine will be titrated weekly either by the patient him- or herself or supervised by a telephone call at the investigator's discretion until the median SMFPG is within target range. The insulin glargine should then be fixed and the median of the last five SMPFG be reviewed at each scheduled visit for being with target range. Should this fall out of range at the review the patient will re-enter weekly titration as written above.

6.5.6.6 Meal insulin: regular human insulin and rapid acting insulin analogues

Initiation of meal insulin is at the investigator's discretion and should only occur if the patient meets the criterion described in section 6.5.6.2.

Novartis will not supply meal insulin as a part of the present study.

Meal insulin may be started as one injection prior to the largest meal of the day for the individual patient adding more doses as needed to maintain glycemic control. Doses should be as directed by the investigator considering minimization of hypoglycemia before the next meal as an important goal.

Should glycemic control improve meal insulin should in principle be discontinued before insulin glargine.

Use of meal insulin must be recorded after start of study drug in the (e)CRF.

6.5.7 Other concomitant treatment

6.5.7.1 Metformin

The goal is that all patients are on maximally tolerated metformin dose within local approved metformin label at the randomization Visit 4 (Month 0) and no less than 1,000mg/day. Patients who enter the study on higher than maximal locally approved dose may continue at that dose.

Novartis will assure supply of metformin extended release, or if not approved locally, immediate release metformin for the duration of the trial through a prescription card or other local country practice as open label medication, not labeled specifically for each patient.

6.5.7.2 Metfomin initiation in drug naïve patients

At Visit 2 (Month -2) patients will initiate metformin extended release at a dose of 1000 mg with the evening meal, or if an extended release formulation is not approved locally 500 mg b.i.d. with two main meals.

This instruction above should be followed as permitted by local guidelines.

6.5.7.3 Metformin titration in drug naïve patients

Metformin will be up titrated weekly with 500 mg following a phone call with the clinic to ensure there is no tolerability or other issues preventing titration.

This titration schedule above should be followed as permitted by local guidelines.

Should metformin be titrated to an intolerable dose, which usually is gastrointestinal side effects, it is permissible to titrate back to the previous tolerated dose. After the Run-in period, starting at Visit 4 (Month 0) metformin dose should be maintained at a constant dose level. Should a patient develop intolerance or decreasing renal function, the dose may be down-titrated following consultation with the sponsor.

6.5.7.4 Restricted medications

Use of any glucose lowering medications except as prescribed per protocol are prohibited for the duration of the study.

Systemic use of immune modulators or local administration sufficient to induce systemic effects should if possible be avoided until Visit 8 (Month 4). There are no restrictions after Visit 8 (month 4).

Any biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, tozilizumab) are prohibited for the duration of the study.

Live vaccines are prohibited during the study and up to three months following the last dose.

6.5.7.5 Other medications

Any untoward adverse events should be treated outside of this protocol according to current local standards of care.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug .

All effort should be made to keep the doses of chronic concomitant medications constant during the 4-Month Dose-Finding Period (e.g., statins, chronic use of aspirin, etc.).

6.5.8 Study drug discontinuation and premature patient withdrawal

Study drug must be discontinued if the investigator determines that continuing it would result in a significant safety risk for that patient. The following circumstances **require** study drug discontinuation:

- Emergence of the following adverse events:
    - Infection qualifying as a Serious Adverse Event
    - At any time during the clinical trial, if ALT and/or AST is greater than or equal to 5 times the ULN without clinical symptoms, the tests must be repeated within 3 days. If confirmed, the patient must be discontinued.

- At any time during the clinical trial, if ALT and/or AST is greater than or equal to 3 times the ULN without clinical symptoms, the test must be repeated within 3 days. If confirmed as being greater than or equal to 3 times the ULN, but being below 5 times the ULN, then the LFT shall be checked every week for the next 4 weeks; if ALT and/or AST remains greater than or equal to 3 times the ULN after 4 weeks, then the patient must be discontinued.
- At any time during the clinical trial, if ALT and/or AST is greater than or equal to 3 times the ULN, with total bilirubin elevated above the ULN, then the patient must be discontinued immediately.

- Withdrawal of informed consent
- Pregnancy and ongoing lactation
- Any other protocol deviation that results in a significant risk to the patient's safety

In addition to these requirements for study drug discontinuation, the investigator should discontinue study drug for a given patient if, on balance, he/she thinks that continuation would be detrimental to the patient's well-being.

If an episode leading to temporary drug discontinuation is resolved, study drug may be resumed. Accurate drug accountability is of essence.

If the study drug discontinuation is permanent, the investigator must complete the Study Drug Discontinuation form, giving the date and primary reason for stopping the study drug.

Patients who discontinue study drug for any reason should not be withdrawn from the study, unless they withdraw consent or are lost to follow-up. If a patient permits, he/she is asked to continue on their current visit schedule until the study is completed.

Patients may voluntarily withdraw from the study for any reason at any time. They will be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion eCRF page. The study completion (Visit 23) and FU Visit must be completed for all patients that prematurely withdraw from the study for any reason.

For patients who are lost to follow-up (i.e. those 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 documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study will not be replaced.

6.5.9 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential for effective treatment of the patient. Most often, study drug 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. When the investigator telephones the system to unblind a patient, he/she must provide the requested patient identifying information.

The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Head that the code has been broken.

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

Study drug must be discontinued after emergency unblinding. Study drug also must be discontinued for any patient whose treatment code has been broken inadvertently or for any non-emergency reason.

6.5.10 Study completion and post-study treatment

When the number of evaluable randomized patients approaches the target number of 600 a notification will be sent to the sites to stop screening further patients at a specific set date. Patients, who have already been screened, will be allowed to continue in the study, if they qualify through the Run-In period.

As described above in section 6.5.8 it is the intent complete all study assessments for as many of the randomized patients as possible irrespective of whether they discontinue study medication. An individual patient is considered completed when he/she completes Visit 23/Month 42 or the study is terminated by the Sponsor.

Patients will continue in the long-term continuation period for a minimum of 24 months and a maximum of 42 months.

The investigator must refer patients for appropriate ongoing care as necessary.

6.5.11 Early study termination

The study can be terminated at any time for any reason by Novartis Pharmaceuticals. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 7 as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to assure 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.

7 Visit schedule and assessments

For Periods I and II of the study, visits are scheduled at screening, Months -2, -1, 0, 1, 2, 3, 4 relative to randomization (Month 0). Thereafter in Period III, visits are scheduled every month until the 4-month primary analysis is completed and all patients are switched into Period IV. In Period IV (Long-term continuation), patients will still return to the clinic for monthly dosing but will only complete other study assessments quarterly at Months 0, 3, 6, etc. until the end of the study.

At the screening visit, Month -1 and visit days that includes a meal challenge test patients should have fasted overnight (i.e. no food or drinks (except water) after 10 pm on the day prior to the scheduled visit). Study visits should occur before 10 am. If the patient has not fasted, the collection of laboratory evaluations must be rescheduled.

Table 7-1, Table 7-2 and Table 7-3 lists all of the assessments and indicates with an "x" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which data are entered into the database (D) or remain in source documents only (S).

Patients should be seen for all visits on the designated day of the month with an allowed "visit window" of ±8 days. Until randomization the visits should be calculated relative to the calendar date of the previous visit month. After randomization visits should be counted relative to the calendar date of the randomization visit.

Patients who permanently discontinue study drug before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit (Visit 23) will be performed regardless of what Study Period the patient is in at the time of discontinuation.

Patients who discontinue study drug should continue in the protocol for all assessments in Table 7-1, Table 7-2 and Table 7-3. If they refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine any adverse events.

At a minimum, patients will be contacted for safety evaluations, capturing any Serious Adverse Events after 3 months following the last dose of study drug or last completed visit (whichever is earlier). Documentation of attempts to contact the patient should be recorded in the patient record.

Table 7-1 Assessment Schedule for Period I and II: Run-in and 4-Month Dose Finding

Visit Number	C[1]	V1	V2	V3	V4	V5	V6	V7	V8
Visit months are relative to randomization		Screen	-2	-1	0 [3]	1	2	3	4
Screening									
Informed Consent	S	x							
Inclusion/Exclusion Criteria	S	x	x		x				
Height	D	x							
Labs for entry criteria only: TSH, GAD, HIV Screen, HBsAg and HCV antibody	D	x							
PPD TB skin test and skin check[2]	S	x							
Demography									
Demography	D	x							
History of Diabetes	D	x							
Medical History / Current Conditions	D	x							
Smoking History	D	x							
Treatment Assessments									
Randomization/Call IVRS	S				x				
Drug Dispensing	S		x	x	x	x	x	x	x
Drug Accountability includes study drug, Metformin and Insulin	D		x	x	x	x	x	x	x
Prior Antidiabetic Medications	D	x							
Concomitant Medications	D		x	x	x	x	x	x	x
Efficacy Assessments									
HbA_{1c}	D	x			x	x	x	x	x
Morning Fasting Plasma Glucose	D	x		x			x		
Fasting Lipid Profile[4]	D	x			x		x		x
Standard Meal Challenge (includes, insulin, C-peptide, glucose)5	D				x				x
Safety Assessments									
Physical Examination	S	x			x				x
Vital Signs	D	x			x				x
Body Weight	D	x			x	x	x	x	x
ECG Evaluation	D	x			x				x
Standard Hematology	D	x			x		x		x
Standard Biochemistry	D	x			x		x		x
Anti-nuclear antibodies (ANA) Screen	D				x				x
Pharmacogenomics	D				x				x
Other Biomarkers[6]	D				x				x
PK/PD/Immunogenicity	D				x	x	x	x	x
Pregnancy Test[7]	D	x							
Urinalysis	D	x			x				x

Visit Number	C[1]	V1	V2	V3	V4	V5	V6	V7	V8
Visit months are relative to randomization		Screen	-2	-1	0 [3]	1	2	3	4
Urinary microalbumin/ creatinine ratio	D	x			x				x
Adverse Events prompting for Cardiovascular Events and Infections	D			x	x	x	x	x	x
Glycemia Study Diary	D		x	x	x	x	x	x	x
Other									
Review 7-Point Glucose Meter Data					x				x
Patient Education[8]	S		x						
Pharmacogenetics sample	D				x				
EuroQoL (EQ-5D)	D		x	x	x				x

[1] C: Category indicates if data are entered into the database (D) or in source documents only (S); all data are supported by source documents.

[2]The skin test check should be done within 48-72 hours after the test. A chest x-ray should be obtained if the PPD skin test results are positive for TB. If the x-ray is also positive, patient must be excluded.

[3] Baseline (Day 1; first day of study medication).

[4] Triglycerides, total cholesterol, calculated LDL, HDL, calculated VLDL, non-HDL cholesterol;

[5] Patients will complete the following before and after the meal ingestion: glucose, insulin, C-peptide at sampling times -20, -10, -1, 10, 20, 30, 60, 90, 120, 150, 180 and 240 minutes. For more details see Section 7.4.2.

[6] A panel of cytokines and chemokines may include but are not limited to: IL-1β,. IL-1ra, IL-6, Anti-ACZ885 Ab, hsCRP, leptin, adiponectin (total and high MW), TNFα, PAI-1 and fibrinogen

[7] Serum pregnancy test for females of child-bearing potential only.

[8] For details regarding Patient Education see Section 7.5.7.2.

Table 7-2 Assessment Schedule for Period III: Intermediate Period

Visit Number	C[1]	V801	V802	V803	V804	V805	V806	V807	V808	V809	V810	V811	V812
Visit months are relative to randomization		**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Treatment Assessments													
Drug Dispensing	S	x	x	x	x	x	x	x	x	x	x	x	X
Drug Accountability includes study drug, Metformin and Insulin	D	x	x	x	x	x	x	x	x	x	x	x	X
Prior Antidiabetic Medications	D												
Concomitant Medications	D	x	x	x	x	x	x	x	x	x	x	x	X
Efficacy Assessments													
HbA_{1c}	D			x			x			x			X
Morning Fasting Plasma Glucose	D						x						x
Fasting Lipid Profile[4]	D						x						x
Safety Assessments													
Physical Examination	S												
Vital Signs	D			x			x			x			x
Body Weight	D			x			x			x			x
ECG Evaluation	D												x
Standard Hematology	D			x			x			x			x
Standard Biochemistry	D			x			x			x			x
Pharmacogenomics	D						x						x
Other Biomarkers[6]	D						x						x
PK/PD/Immunogenicity	D												
Pregnancy Test[7]	D												
Urinalysis	D						x						x
Urinary microalbumin/ creatinine ratio	D						x						x

Visit Number	C[1]	V801	V802	V803	V804	V805	V806	V807	V808	V809	V810	V811	V812
Visit months are relative to randomization		**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Adverse Events prompting for Cardiovascular Events and Infections	D	x	x	x	x	x	x	x	x	x	x	X	x
Glycemia Study Diary	D	x	x	x	x	x	x	x	x	x	x	X	x
Other													
EuroQoL (EQ-5D)	D			x			x			x			x

[1] C: Category indicates if data are entered into the database (D) or in source documents only (S); all data are supported by source documents.

[4] Triglycerides, total cholesterol, calculated LDL, HDL, calculated VLDL, non-HDL cholesterol

[6] A panel of cytokines and chemokines may include, but are not limited to: IL-1β, IL-1ra, IL-6, Anti-ACZ885 Ab, hsCRP, leptin, adiponectin (total and high MW), TNFα, PAI-1 and fibrinogen

[7] Serum pregnancy test for females of child-bearing potential only.

Table 7-3 Assessment Schedule for Period IV: Long-term Continuation Period

Visit Number	C[1]	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24
Visit months are relative to study drug switch		**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42[10]**	**F/U**
Treatment Assessments																	
Drug Dispensing[9]	S	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Drug Accountability[9] includes study drug, Metformin and Insulin	D	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant Medications	D	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Efficacy Assessments																	
HbA_{1c}	D	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Morning Fasting Plasma Glucose	D			x				x				x					
Fasting Lipid Profile[4]	D	x		x		x		x		x		x		x		x	
Standard Meal Challenge (includes, insulin, C-peptide, glucose)[5]	D	x				x				x				x		x	
Safety Assessments																	
Physical Examination	S															x	
Vital Signs	D	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Body Weight	D	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECG Evaluation	D	x				x				x				x		x	
Standard Hematology	D	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Standard Biochemistry	D	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Anti-nuclear antibodies (ANA) Screen	D	x				x				x				x			
Pharmacogenomics	D	x		x		x		x		x		x		x		x	
Other Biomarkers[6]	D	x		x		x		x		x		x		x		x	

Visit Number	C[1]	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22	V23	V24
Visit months are relative to study drug switch		**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42[10]**	**F/U**
PK/PD/Immunogenicity	D			x													
Pregnancy Test[7]	D															x	
Urinalysis	D	x		x		x		x		x		x		x		x	
Urinary microalbumin/ creatinine ratio	D	x		x		x		x		x		x		x		x	
Adverse Events, prompting for Cardiovascular Events and Infections	D	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[11]
Glycemia Study Diary	D	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Other																	
Review 7-Point Glucose Meter Data	D	x				x				x				x		x	
EuroQoL (EQ-5D)	D	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Study Completion	D															x	

[1] C: Category indicates if data are entered into the database (D) or in source documents only (S); all data are supported by source documents.

[5] Patients will complete the following before and after the meal ingestion: glucose, insulin, C-peptide at sampling times -20, -10, -1, 10, 20, 30, 60, 90, 120, 150, 180 and 240 minutes. For more details see Section 7.4.2.

[6] A panel of cytokines and chemokines may include but are not limited to: IL-1β, IL-1ra, IL-6, Anti-ACZ885 Ab, hsCRP, leptin, adiponectin (total and high MW), TNFα, PAI-1 and fibrinogen

[7] Serum pregnancy test for females of child-bearing potential only.

[9] Patients will return to the clinic monthly for study drug injections throughout the 4 year long term continuation period. They will have other study assessments done quarterly.

[10]This visit is to be done for all patients when they complete the study or withdraw from the study early. The Study Drug Discontinuation Form will be completed in the CRF at the time the patient discontinues study drug, regardless of whether the patient remains in the study or not.

[11] Only Serious Adverse Events will be recorded at this Follow-up Phone Call Visit. This visit should be done three months after the patient discontinues study drug or completes the study, whichever is earlier.

7.1 Information to be collected on screening failures

Patients may discontinue from the study prior to randomization from Visit 1 through Visit 4 or at Month 0, prior to any double-blind medication being administered. These patients discontinuing prior to randomization are considered screening failures.

If a patient discontinues before entering the double-blind treatment period, only the demographic information and Screening Log entry with the primary reason for discontinuation should be completed on the eCRF. It is not necessary to complete all the required evaluations at the time of discontinuation unless medically indicated.

Also, all Serious Adverse Events will be reported to Novartis from the time the patient signs informed consent, even if occurring during the Screening/Run-In Period.

7.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, ethnicity and source of patient referral.

All relevant medical history will be collected at Visit 1. General medical history will include organ system classes: HEENT, Neoplastic and Hematological Disorders, Cardiovascular with subcategories for family history (yes/no), prior events or disease, hypertension (year of diagnosis), hyperlipidemia (year of diagnosis), smoking history (cigarettes: start, stop, amount in pack years; cigars: start, stop, amount in cigars per week; pipe: start, stop, amount in pipes per week), Respiratory, Kidneys and Urinary Tract, Gastrointestinal, Immunological and infectious disease with specific questions for prior pyogenic infections requiring antibiotics, Endocrine and Metabolic including history of diabetes and complications (date of diabetes diagnosis; whether proliferative retinopathy, non-proliferative retinopathy, nephropathy, neuropathy and foot ulcers are present and their respective start dates), CNS including psychiatric disorders. Relevant medical history/current medical condition data includes data until the start of study drug. Where possible, diagnoses and not symptoms will be recorded.

7.3 Treatment exposure and compliance

During Study Periods II, III and IV study drug will be administered at the clinic under the supervision of the investigative staff and the dosing record will be captured in the Dosage Administration Record page of eCRF.

Information regarding metformin treatment prior to the study entry, including the start date, the most recent daily dose and its start date will be collected on the 'History of Metformin Dosage Administration' eCRF. The daily dose of metformin treatment after randomization will be captured in the Dosage Administration Record page of eCRF. Compliance will be assessed by the investigator and/or study personnel at each visit based on information provided by the patient.

Use of insulin glargine, including starting date and daily total dose (U) will also be captured in the Dosage Administration Record page of eCRF.

All antidiabetic (glucose lowering) medications other than metformin are prohibited prior to study enrollment. Any short-term treatment course with insulin in connection with a hospitalization, etc. within 12 months of Visit 1 along with most recent total daily dose, unit, route, and start and end date for the medication will be recorded on the Antidiabetic Medications eCRF.

All medications other than metformin or insulin taken after the start of blinded study drug, the reason for prescribing the medication, and the start and end dates will be recorded on the Concomitant Medications / Significant Non-drug Therapies eCRF.

7.4 Efficacy

Efficacy parameters will be assessed at various time points during the study. See Section 10 Data Analysis for details of the analysis. The following efficacy measurements will be measured at various timepoints during the study (see Table 7-1, Table 7-2 and Table 7-3):

- HbA_{1c} measured by NGSP certified methodology
- FPG
- Fasting Insulin
- Fasting Lipids

Other efficacy measurements are outlined below.

7.4.1 Duration and Dose of Insulin Rescue Treatment

Insulin rescue by the established criteria in Section 6.5.6 and dose will be tracked at every visit.

7.4.2 Standard mixed liquid meal test

A standard liquid mixed-meal challenge will be done at baseline (Visit 4/Month 0), Month 4, every year during Period IV and the end of study visit. Patients should have fasted overnight (i.e. no food or drinks (except water) after 10 pm on the day prior to the scheduled visit). Study visits should occur before 10 am. If the patient has not fasted, the collection of laboratory evaluations must be rescheduled. Patients will complete each standard meal challenge with measurement of the following variables prior to and after meal ingestion: glucose, insulin, and C-peptide at sampling times -20, -10, and -1, 10, 20, 30, 60, 90, 120, 150, 180 and 240 minutes relative to the start of a liquid mixed meal. The meal has to be completed in five minutes. Throughout the standard meal challenge, patients will not be allowed any other food, or any caloric or xanthine (e.g. caffeine) containing beverages. Water is permitted during the challenge. Smoking will not be allowed through out the standard meal challenge.

The liquid meal consumed will be Nestle Boost Plus. Boost Plus is 360 calories per 8-oz serving. Boost Plus has 1.52 kcal/mL and is lactose-free, kosher and gluten-free. For more details regarding ingredients refer to the packaging label.

Fasting plasma glucose, insulin and C-peptide will be used for HOMA2-B, HOMA2-IR and QUICKI index (Chen H et al, 2005). The time profile of postprandial glucose, insulin and C-

peptide will be assessed as measures of β-cell response to stimulation. Assessments of insulin secretion and sensitivity parameters will be made using postprandial glucose and C-peptide simultaneously.

7.4.3 Appropriateness of efficacy measurements

The efficacy variables selected are standard assessments of the effect of an investigational medicine on glycemic control, β-cell function and insulin sensitivity in T2DM patients.

HbA_{1c} is an integrated measure of average glucose concentration in plasma in the last 2-3 months and as such is a good measure of immediate consequences of improved β-cell function and/or insulin sensitivity. Due to the need to treat patients and the addition of other therapies affecting HbA_{1c}, it does not work well to demonstrate deterioration over longer periods of time.

The need for rescue medication by set criteria as well as the insulin dose required serves as good proxy for deteriorating diabetes over time and is used as the primary variable in period IV of the study.

The assessments of insulin secretion will give preliminary information about whether canakinumab works primarily through improving β-cell function or modulating insulin sensitivity. The meal test is the best available methodology that can give reasonably accurate and precise estimates of these parameters in the dynamic state in medium scale studies like the present one.

7.5 Safety

7.5.1 Physical examination

A complete physical examination will be performed at Screening and Months 0, 4, and the end of the study. It 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 the start of study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's eCRF.

7.5.2 Vital signs

Vital signs will be assessed at Screening, and Months 0, 4 and every three months until the end of the study. This will include BP and pulse measurements. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the last two measurements will be used (disregarding

the first measure). In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

7.5.3 Height and weight

Height in centimeters (cm) will be measured at Screening.

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at Screening and Months 0, 1, 2, 3, 4 and every three months thereafter until the end of the study or premature discontinuation.

7.5.4 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.

7.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured at Screening and Months 0, 2, 4 and every three months thereafter until the end of the study or premature discontinuation.

7.5.4.2 Clinical chemistry

Blood urea nitrogen, serum creatinine, total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, total protein, albumin, and uric acid will be measured at Screening and Months 0, 2, 4 and every three months thereafter until the end of the study or premature discontinuation.

7.5.4.3 Urinalysis

Dipstick measurements for specific gravity, protein, glucose and blood will be done. WBC and RBC sediments will also be measured. A urine sample will also be sent to the Central Lab for testing the urine microalbumin.

7.5.4.4 Anti-nuclear antibodies (ANA) Screen

Blood will be obtained for an anti-nuclear antibodies (ANA) screen during Period II at the Randomization Visit and Month 4 (Visit 8) and during Period IV at Months 0, 12, 24, 36 and 42 (End of Study).

7.5.4.5 Laboratory Evaluations Table

Hematology	Biochemistry	Urine Measurements
Red Blood Cells Platelet Count Hemoglobin Hematocrit White Blood Cells with Differential	Sodium Potassium Chloride Calcium Phosphorous Blood urea nitrogen (BUN) Serum Creatinine (SCr) Total Bilirubin AST ALT Alkaline phosphatase Total protein and albumin Uric Acid Fasting Lipids Triglycerides: Cholesterol (total, HDL, LDL, VLDL, non-HDL)	Urinalysis Urine microalbumin (calculate urinary microalbumin/creatinine ratio) Other Lab Assessments HbA_{1c} Fasting plasma glucose Insulin C-peptide Serum Pregnancy Test Anti-nuclear antibodies (ANA) Screen TSH* GAD* Hepatitis B surface antigen (HBsAg)* HCV antibodies* HIV*

*Assessed at Visit 1 only

Refer to Table 7-1, Table 7-2 and Table 7-3 Assessment schedules for laboratory time-points

7.5.5 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed and evaluated locally with equipment available at the site. It will be done at Screening and Months 0, 4 and yearly thereafter until the end of the study or premature discontinuation visit. Each ECG tracing should be labeled with the study number, patient initials, patient number, date, and kept in the source documents at the study site. Interpretation of the tracing must be made by a qualified physician and clinically significant abnormalities should be reported in the eCRF. Clinically significant abnormalities should also be recorded on the relevant medical history/Current medical conditions eCRF page prior to randomization. Clinically significant findings at Screening must be discussed with the Novartis Medical Monitor prior to enrolling the patient in the study. New findings at any visit must be carefully followed up for evaluation as a cardiovascular adverse event.

7.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test at Screening and the end of the study. Any suspicion of pregnancy during the study must be followed up with an extra serum pregnancy test, which if positive requires immediate interruption of study medication.

7.5.7 Hypoglycemic events

Hypoglycemic events or symptomatology reported by the patient on the diary and evaluated by the investigator to be caused by decreases in glucose available to tissues even if accompanied by a self monitored glucose value above the definition threshold will be reported on a specific form for this purpose. Hypoglycemic events will only be reported as adverse events if they are accompanied by coma and/or seizure and will as such be reported as serious adverse events.

7.5.7.1 Severe hypoglycemia definition and criteria for reporting as serious adverse events

A hypoglycemic event is defined as severe when the following criteria are met:

- Requirement for third party assistance to recognize and/or treat hypoglycemia due to impaired consciousness of the patient

and a confirmation with can be either

- a glucose meter measured plasma glucose concentration < 2 mmol/L (36 mg/dL), or
- prompt recovery upon treatment with carbohydrate or glucagon

Merely getting help without a requirement for it does not qualify an event as severe.

Only severe hypoglycemic events accompanied with coma and/or seizure will be reported as serious adverse events in addition to being reported as severe hypoglycemic events.

7.5.7.2 Patient Education

At Visit 2, patient education regarding hypoglycemic symptoms and treatment should occur. This education should include:

1. General review of hypoglycemia including
    - explanation of possible triggers of hypoglycemia (e.g., strenuous exercise, delayed meals)
    - identification of the symptoms of hypoglycemia (e.g., adrenergic symptoms such as tachycardia, palpitations, shakiness, cholinergic symptoms such as sweating, central symptoms such as dizziness, hunger, blurred vision, impairment of motor function, confusion or inappropriate behavior).
    - review of appropriate treatment for events (oral carbohydrate intake).
2. Explanation of the use of a home glucose monitor. A home glucose monitor will be provided with all appropriate supplies. Blood glucose should be measured every time the patient experiences symptoms which may be suggestive of hypoglycemia, as well as other timepoints which may be recommended by the investigator. The home glucose monitors should be calibrated appropriately.
3. Review of the Study Diary.
    - Any time the patient experiences symptoms which he/she suspects are related to hypoglycemia, the patient should be instructed to take a blood glucose measurement and treat the event as appropriate. Patients should record the event in the study diary,

including the glucose value, any relevant associated information, time of occurrence in relation to the last medication and to the last meal intake, the treatment used and the response to it.

- Additionally, if a patient performs routine measurements of blood glucose, any asymptomatic plasma glucose <3.1 mmol/L (56 mg/dL) which corresponds to a whole blood glucose level <2.8 mmol/L (50 mg/dL) should be treated and recorded in the Study Diary.
- Return the Study Diary at the next scheduled visit.

7.5.7.3 Data collection

The Study Diary will include all the necessary fields to assess each hypoglycemic event for severity and seriousness using as extensive use of tick or circling choice item as practicable to facilitate reporting compliance. Completed diaries will be reviewed at each visit with the study coordinator and each episode suspected of being caused by hypoglycemia or falling available glucose will be reported on the eCRF irrespective of whether a glucose measurement is available or not.

7.5.8 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

7.6 Other assessments

7.6.1 7-Point Glucose Meter Testing

Patients will be asked to check their glucose level (7 times) using their glucose meter on one of the seven days prior to the Meal Challenge Visits (Period 1: Month 0, Month 4, Period IV: Month 0, 12, 24, 36, 42). The patient will document the results (including whether they tested plasma or blood) in their Study Diary. The patient should be instructed to test at the following timepoints: fasting before breakfast, 2 hours after starting breakfast, before lunch, 2 hours after starting lunch, before dinner, 2 hours after dinner and at bedtime.

7.6.1.1 Data collection

The Study Diary will include all the necessary fields to collect the date/time and result of the self-monitored glucose level and will include whether the patient is testing plasma or blood. Completed diaries will be reviewed at each visit with the study coordinator who will be responsible for capturing the data in the eCRF. The study diary will be kept in with the patient's source documents.

7.6.2 Health-related Quality of Life

Patient Reported Outcomes

Generic multidimensional health-related quality of life will be assessed with the EuroQoL (EQ-5D). The EuroQol EQ-5D is a simple but effective standardized instrument designed for use as a measure of health outcome. Applicable to a wide range of health conditions and

treatments, it provides both a compact descriptive profile and a single index value that can be used in the clinical and economic evaluation of health care.

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

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

Data capture

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

Health State Classification

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

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

Visual Analogue Scale 'Thermometer'

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

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

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

Missing or ambiguous values will be left blank.

Note: Questionnaire should be completed by the patient at the center before any other assessments take place. It will be done as per the Schedule of Assessments (Table 7-1, 7-2, 7-3)

7.6.3 Pharmacokinetics, Pharmacodynamics and Immunogenicity

Blood samples for assessing population pharmacokinetics, pharmacodynamics and immunogenicity will be drawn prior to dosing at Months 0, 1, 2, 3, 4 and during the Long-Term Continuation (Period IV) at Month 6.

In case of an anaphylactic reaction after injection should occur, a PK and Immunogenicity sample will be taken at the time of the event and 8 weeks later.

Blood collection (serum)

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein (opposite arm to that used for drug administration). For each scheduled collection, 6 ml blood will be drawn into a plain barrier tube, to obtain serum for both PK and PD (IL-1β) and immunogenicity (anti-ACZ885 antibodies)

- Aliquot 1 (400 µl): PK
- Aliquot 2 (400 µl): PK back-up sample
- Aliquot 3 (500 µl): IL-1β
- Aliquot 4 (remainder, approx. 500 µl): IL-1β back-up sample
- Aliquot 5 (400 µl): Anti-ACZ885 Ab
- Aliquot 6 (400 µl): Anti-ACZ885 Ab back-up sample

For a detailed description of blood sampling schema, please refer to the Blood Collection Log in Appendix 3. All samples will be given a unique sample number (as listed in Appendix 3). The actual sample collection date and time will be entered on the PK blood collection page of the eCRF. Sampling problems will be noted in the Notes field of the eCRFs.

Also refer to the Lab Manual for more details on sample collection and processing.

Analytical method(s)

ACZ885 will be analyzed in serum by means of a competitive ELISA assay, lower limit of quantification (LLOQ) at 100 ng/mL.

Details of the analytical methods to assess ACZ885 in serum will be described in the bioanalytical data report.

7.6.4 Pharmacogenetics

The Study includes an optional pharmacogenetic component which requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents these options to the patient.

Exploratory pharmacogenetics research studies are planned as a part of this study with the objectives of identifying inherited genetic factors which may (1) be related to type 2 diabetes, (2) predict response to treatment with ACZ885, (3) predict relative susceptibility to drug-drug interactions, or (4) predict genetic predisposition to side effects. We hope to develop a better understanding of type 2 diabetes and how patients respond to ACZ885.

Pharmacogenetic analysis will be done to identify genetic polymorphisms potentially related to the clinical response following canakinumab treatment. A single blood sample (10 ml) will be collected at Baseline (Visit 4/ Month 0). Further sample collection instructions will be outlined in the Lab Manual.

Despite continuing advances in genetics research, not all of the polymorphisms relevant to drug metabolism, drug action and type 2 diabetes have been identified. Therefore, additional polymorphisms will be added within the restricted scope of these studies as described above.

7.6.5 Pharmacogenomic sample collection and procedures

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

Two 2.5 mL blood samples will be collected in PAXgene tubes at as per the Assessment Schedule (Table 7-1, Table 7-2 and Table 7-3).

Sample collection will be outlined in the Lab Manual.

7.6.6 Other biomarkers

Soluble protein markers related to the target pathway and diabetic disease markers, such as IL-1β, IL-1ra, IL-6, Anti-ACZ885 Ab, hsCRP, leptin, adiponectin (total and high MW), TNFα, PAI-1 and fibrinogen may be measured, among others. Instructions for collection and processing of these samples will be outlined in the Lab Manual. See Assessment Schedule (Table 7-1, Table 7-2 and Table 7-3) for timepoints of collection.

8 Safety monitoring

8.1 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any period of the study. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient 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. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- 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 the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- is a hypoglycemic event accompanied by coma and/or seizure

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8-2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. 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, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the 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.

8.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 90 days after the patient has stopped study participation must be reported to Novartis within 24 hours of learning of its 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.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Integrated Medical Safety (IMS) Department. The telephone and telecopy number of the contact persons in the local department of Integrated Medical Safety (IMS), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. 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 Integrated Medical Safety (IMS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug 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 Integrated Medical Safety Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be delegated for this study. This Board will be comprised of Novartis personnel not directly involved with the study and external experts. The DMC will convene at pre-specified intervals as outlined in the DMC Charter. This will occur at a minimum after data has been assembled when all patients complete the dose finding period of the study (Period II). The DMC will also review the long-term safety experience of ACZ885 at pre-specified intervals.

In addition, ongoing review of adverse events, including clinical laboratory data will be continuously reviewed by the Novartis medical monitor and, as indicated, by the Novartis pharmacovigilance team.

8.5 Adjudication committees

Program wide cardiovascular clinical events will be reviewed under blind by an independent cardiovascular adjudication committee, composed of at least two outside reviewers. This measure is designed to ensure the objectivity, reliability and validity of the event classification. The procedures for reporting and case definitions are detailed in a separate charter document (Investigator Guidelines).

Similarly, program wide infectious clinical events and malignancies will be reviewed under blind by an independent adjudication committee, composed of at least two outside reviewers.

9 Data review and database management

9.1 Site monitoring

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

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on (e)CRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the (e)CRFs. 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.

An unblinded monitor will also be assigned at each site to review the drug accountability and dispensing records maintained by the unblinded pharmacist/nurse/physician.

9.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

9.3 Database management and quality control

The CRO working on behalf of Novartis will 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. Obvious errors are corrected by the CRO working on behalf of Novartis. 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 using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. 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 the CRO designated by Novartis.

Randomization codes and treatment assignment to the patient will be tracked using an Interactive Voice Response System. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis or a CRO designated by Novartis.

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

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

Diary data will be entered into paper diary by the patient. At the patient visit, the glycemia study diary will be used by the designated investigator staff to transcribe details of hypoglycemic events onto the relevant eCRF page (s). The paper diary will then be filed with the source documents at the Investigator site.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis. The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete 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 Global Head of Biostatistics and Statistical Reporting and the Global Therapeutic Area Head.

10 Data analysis

10.1 Populations for analysis

Period II Assessments

The **Full Analysis Set** (FAS) includes all randomized patients with the exception of mis-randomized patients. Mis-randomized patients refer to patients who are not qualified for randomization but were inadvertently randomized into the study and did not receive study drug. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

The **Per Protocol Set** (PPS) includes all patients who completed Period II without protocol deviations likely to have a substantial effect on the primary variable.

The **Safety Population** (SAF) includes all patients who received at least one dose of study medication during Period II. Patients will be analyzed according to treatment received. Of note, the statement that a patient had no adverse events also constitutes a safety assessment.

Period III and IV Assessments

The **Full Analysis Set** (FAS) includes all patients who enter into the respective period. Patients will be analyzed according to treatment received.

The **Safety Population** (SAF) includes all patients who received at least one dose of study medication during the respective period. Patients will be analyzed according to treatment received.

10.2 Patient demographics/other baseline characteristics

Demographic, background data and key efficacy variables at baseline will be summarized for all randomized patients by treatment group using frequency tables for qualitative variables

(gender, race, age group, body mass index group, metformin dose group, and baseline HbA_{1c} group; groupings as for the subgroups described in Section 10.5), and mean, standard deviation, median, minimum and maximum for quantitative variables (age, height, weight, body mass index, duration of type 2 diabetes, metformin dose at randomization and baseline HbA_{1c} and FPG).

Body mass index (BMI) will be calculated from the collected variables height and weight at Visit 1. Baseline HbA_{1c} and FPG are the values obtained at randomization (Visit 4/Month 0) or at screening (Visit 1) if Visit 4 values are missing.

The demographic and baseline data will be tabulated for the dose-finding period (Period II) and for the long-term treatment period (Period IV) separately by respective treatment group.

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

The duration of exposure to study drug during the dose-finding period (Period II) and the long-term treatment period (Period IV) will be separately summarized by respective treatment group for all randomized patients. The exposure during the intermediate period (Period III) will also be summarized by treatment group. The duration of exposure to metformin will be summarized similarly. For patients receiving insulin treatment in Period III or Period IV, the duration of insulin treatment will also be summarized by treatment period.

10.4 Analysis of the primary objective(s)

10.4.1 Variable

The primary efficacy variable for the dose finding period (Period II) is the change from baseline in HbA_{1c} at Month 4.

10.4.2 Statistical hypothesis, model, and method of analysis

For the dose finding period (Period II), the primary hypotheses to be assessed are:

- $H_{o1}: \delta_{ACZ\ 5\ mg} = \delta_{placebo}$ versus $H_{a1}: \delta_{ACZ\ 5\ mg} \neq \delta_{placebo}$,
- $H_{o2}: \delta_{ACZ\ 15\ mg} = \delta_{placebo}$ versus $H_{a2}: \delta_{ACZ\ 15\ mg} \neq \delta_{placebo}$,
- $H_{o3}: \delta_{ACZ\ 50\ mg} = \delta_{placebo}$ versus $H_{a3}: \delta_{ACZ\ 50\ mg} \neq \delta_{placebo}$,
- $H_{o4}: \delta_{ACZ\ 150\ mg} = \delta_{placebo}$ versus $H_{a4}: \delta_{ACZ\ 150\ mg} \neq \delta_{placebo}$,

Where δ is the change from baseline in HbA_{1c} at Month 4 in the treatment group indexed by the subscript. An analysis of covariance (ANCOVA) followed by two-sided Dunnett's test for multiple comparisons with a control will be used for the comparison of each active dose versus placebo. The ANCOVA model will include treatment and Metformin dose category (<1500mg and $\geq$ 1500mg daily) as the classification variables and baseline as the covariate. Nominal 95% confidence interval for the estimated difference between each active dose and placebo will also be determined based on the ANCOVA model. Continuous dose response models, including linear, quadratic, Emax and others, will be explored and assessed using Akaike Information Criterion (AIC). Hypothesis testing of non-constant dose response curve

and estimation of doses achieving target clinical effects will also be performed using MCP-Mod method (Bretz F et al 2005); details will be provided in analysis plan).

10.4.3 Handling of missing values/censoring/discontinuations

For the dose finding period (Period II), the full analysis set (FAS) will be the primary analysis population. The last observation carried forward (LOCF) method will be used for patients without Month 4 HbA_{1c} measurement for any reason as well as for patients who require rescue medication or use any other glucose lowering agents other than metformin. A sensitivity analysis will also be conducted using other methods of imputation besides LOCF (details will be provided in analysis plan).

10.4.4 Supportive analyses

The analysis for the primary efficacy data of Period II will also be performed for the per protocol set (PPS).

For the dose finding period (Period II), subgroup analysis based on categories of baseline HbA_{1c} category ($\leq 8\%$, $>8\%$), BMI (< 30 kg/m^2, ≥ 30 kg/m^2 at Visit 1), age (< 65 years, ≥ 65 years at Visit 1), prior use of metformin, metformin dose (<1500mg and $\geq$ 1500mg daily), geographic region, gender, and race may be performed by including interaction terms in the ANCOVA model wherever sample size warrants. The HbA_{1c} responder analysis (Month 4 $HbA_{1c} < 7\%$) will be performed using logistic regression.

10.5 Analysis of secondary objectives

10.5.1 Efficacy (secondary)

For the dose finding period (Period II), ANCOVA followed with Dunnett's test on change from baseline described in Section 10.4.2 will also be used for analyzing the secondary efficacy variables include fasting plasma glucose (FPG), insulin, HOMA B, HOMA IR, and QUICKI index. The change from baseline in average glucose level and peak glucose level derived from self-administered seven (7) point glucose profiles will be analyzed similarly. The change from baseline in hsCRP (in log scale) will be analyzed using ANCOVA model. Supportive analyses using nonparametric approach or categorical approach may also be performed. Exploratory efficacy variables of percentage change from baseline in fasting lipids (triglycerides, total cholesterol, LDL, HDL) will be analyzed using ANCOVA in appropriate scale.

Efficacy variables derived from the meal test, including area under the 0-4 hour prandial curve ($AUC_{0\text{-}4hr}$) plasma glucose, insulin and C-peptide values, the 2-hour absolute glucose level as well the peak value of plasma glucose, insulin and C-peptide values will also be analyzed using ANCOVA models. Insulin secretion rate (ISR) using deconvolution of post-challenge glucose and C-peptide will be derived and analyzed.

Efficacy data collected during the transition period (Period III), including insulin use, will be summarized by dose group and by monthly interval since Month 4.

For the long-term treatment period (Period IV), the duration of rescue insulin use and insulin dose will be key efficacy variables. The duration of rescue insulin use, as a ratio to Period IV treatment duration, will be compared between the active and placebo treatment groups using nonparametric approach. The patients' individual duration of Period III, the dose of ACZ885 and use of insulin during Period III will be taken into considerations as covariates. Similarly, the insulin dose at Month 6, 12, 18, and 24 will be compared between the active and placebo treatment groups.

As an exploratory analysis, the events of insulin treatment initiation or subsequent events of insulin dose increase after initial insulin titration period will be considered as treatment failures. The incidence of such treatment failures will be explored using appropriate survival analyses methods. Multiple event analysis will be used if the number of rescue medicine events/dose adjustment events is large enough to perform the analysis.

All other efficacy variables assessed during Period IV, including prandial glucose, C-peptide, insulin, insulin secretion rate, HbA_{1c}, FPG, hsCRP, lipids will also be analyzed using ANCOVA models in appropriate scale with insulin use and duration and ACZ885 dose of Period III taken into considerations as covariates (details will be provided in analysis plan).

10.5.2 Safety

The assessment of safety will be based primarily on the frequency of adverse events (AEs), laboratory abnormalities and serious adverse events (SAEs) for the safety set (SAF). Serious adverse events suspected by the investigators to be related to the study medications and other safety data (e.g., body weight) will be summarized as appropriate.

For a given treatment period in this study (Period II, Period III and Period IV), the only adverse events that will be counted for that treatment will be treatment-emergent events. These events are those that started after the start of that treatment period, or were present at the start of the treatment period but increased in severity, changed from being not suspected to being suspected to study drug, or developed into an SAE after the start of the treatment period. However, an overall incidence (both first event and total events) per person year follow-up for each dose across all treatment periods will be determined as part of the long-term safety database.

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. In addition, the incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term. SAEs, if any, will be narrated.

Adverse events related to major cardiovascular events (MACE), serious infections and hypoglycemia will be specifically investigated. The incidence of hypoglycemia will be tabulated separately for patients with or without rescue insulin treatment and analyzed using Poisson regression.

Laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), summary statistics of raw data and change from baseline (mean, medians, standard deviations, ranges) and by flagging of notable values in data listings.

Data from other tests (e.g., immunogenicity, electrocardiogram (ECG) or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Body weight data will be analyzed using ANCOVA.

Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further considerations.

10.5.3 Health-related Quality of Life

Health state classification will be converted to a score (during data analysis stage) according to a list provided. This list has 243 values for all possible EuroQoL health status. For example a health state of 11111 will have a score of 1.00 and a health status of 12132 will have a score of 0.09 (Rabin and deCharro 2001).

The primary analysis will be the estimation of weighted indices over time for patients in each treatment group. These may be depicted graphically against the population values. The change in average VAS scores will also be tabulated.

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

10.5.4 Pharmacokinetics

A mixed effects modeling approach will be used to characterize the PK of canakinumab and it's binding to IL-1ί; the model structure is identical to that described in the CACZ885A2101 modeling report.

PK parameters such as CL/F, Ka and V/F and their associated variability will be estimated, as well as parameters describing the PK of IL-1ί, such as rate of production, clearance, and its binding affinity to canakinumab. The relationship between population parameters such as CL/F and covariates such as dose, age, and weight may be investigated using graphical methods and simple regression models. If the data is not sufficient for analysis, it may be pooled with predefined data from other canakinumab studies.

10.5.5 Pharmacogenetics/pharmacogenomics

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. SNPs variation will be analyzed for their correlation to response to treatment or to disease activity. A range of statistical tests (chi-square tests, ANCOVAs, linear and logistic regression) are used for the analyses. Additional data, from subsequent clinical trials, are often needed to confirm associations. Alternatively, if the numbers of patients enrolled in the study are too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

For pharmacogenomics, messenger RNA (mRNA) will be extracted from blood samples. mRNA will be analyzed for gene expression using gene expression microarrays such as Affymetrix microarray technology and/or quantitative RT-PCR. Quality control of all

individual RNA samples and expression data will be conducted. The gene expression data will be analyzed using several different algorithms including various clustering analysis algorithms, ANOVA correlation analysis, and different filtering strategies based on magnitude and statistical significance of differences of gene expression.

10.5.6 Biomarkers

Soluble protein marker studies investigate differences in the level of expression of proteins or peptides between individuals in a given biofluid. The goal of such studies is to allow the identification of potential protein or peptide biomarkers of drug action, response to drug, or disease, and to better understand the associated underlying molecular mechanisms. By applying statistical analysis methods (e.g. principal component analysis) between subject groups, distinct study time points, or between subject groups, it may be possible to identify patterns which are associated with disease state or response to drug treatment. However, the exact type of data analysis method will depend on the type of data obtained in the study and is difficult to specify in advance. Consequently, analysis of this information will be data driven.

10.5.7 PK/PD

Exploratory analysis of the relationship between PK and efficacy variables will be carried out as a separate activity.

10.6 Sample size calculation

The primary objective of the study, dose finding, will be based on change from baseline in HbA_{1c} at Month 4. Comparison of each dose versus placebo will be performed using analysis of covariance followed by Dunnett's multiple comparison procedure. The study at a sample size of N=100 for each dose group and N=200 for the placebo group will have an ≥80% power to demonstrate at least one active dose is significantly different from placebo, i.e. rejecting at least one of the hypotheses H_{01}, H_{02}, H_{03}, and H_{04}, when one or more of the active doses truly differ from placebo in HbA_{1c} by 0.41 at an overall α level of 0.05 (two-sided) with Dunnett's test. The assumed population standard deviation is 1 for the sample size calculation.

10.7 Power for analysis of critical secondary variables

For the long-term part of the study, a total of 260 patients in the combined active group and 130 patients in the placebo group are expected to complete the 24 months treatment, assuming an attrition rate of 35% over two years as suggested by historical data. This sample size will provide ≥80% power for the study to detect an increase of event rate of 7%, 12%, 14%, and 16% in the active group as compared to placebo group (absolute difference) if the event rate in the placebo group is ≤1%, 10%, 20%, and from 30% to 50%, respectively, at a nominal α level of 0.05 (two-sided) using Fisher's exact test.

10.8 Interim analysis

When the last randomized patient completes the dose finding treatment period (Period II), analyses of unblinded efficacy and safety data will be performed for the purpose of dose

selection. As dose finding is the primary objective of the study, this will not be deemed as an interim analysis. However, to minimize potential bias in study conduct for the long-term continuation period of the study, the dose finding results will not be widely disseminated. Patients, investigative staff, sponsor personnel with direct contact with sites, and adjudication committee members will remain blinded to treatment identity throughout Period IV. Unblinded Novartis personnel without direct contact with sites will be responsible for the primary analysis procedures.

A futility analysis may be conducted after 300 patients completing the 4-month dose finding period, unless by this time recruitment has already been completed. A predictive power approach may be used to evaluate futility in efficacy. Dose(s) for which the interim data suggest extremely low probability of success (threshold will be pre-specified should futility analysis is to take place) even with full recruitment may be stopped and the unfulfilled sample size will then be transferred equally to other dose groups. Patients who were already randomized to the dose(s) will also be transferred equally to other dose groups.

11 Ethical considerations

11.1 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.

11.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-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/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.3 Responsibilities of the investigator and IRB/IEC/REB

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

11.4 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 trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12 Protocol adherence

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

12.1 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/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the

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

13 References

Available Upon Request

[Bretz F, Pinheiro JC, Branson M (2005)] Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics; 61:738.

[Chen H, Sullivan G, Quon MJ (2005)] Assessing the predictive accuracy of QUICKI as a surrogate index for insulin sensitivity using a calibration model. Diabetes; 54:1914.

[Gerich (2003)] Contributions of Insulin-Resistance and Insulin-Secretory Defects to the Pathogenesis of Type 2 Diabetes Mellitus. Mayo Clinic Proc.; 78:447-456.

[Lachmann HJ, Jung T, Bobadilla M, et al (2006)] Treatment of Muckle Wells Syndrome with a fully human anti-IL-1β monoclonal antibody (ACZ885) – initial results from a proof of concept study. Ann Rheum Dis;65(Suppl II):76.

[Lachmann HJ, Lowe P, Offer M, et al. (2008)] Treatment of cryopyrin associated periodic fever syndrome with a long-acting fully human anti-IL-1beta monoclonal antibody (ACZ885) [abstract]. Ann Rheum Dis; 67(Suppl II):49.

[Larsen CM, Faulenbach M, Vaag A, et al (2007)] Interleukin-1-Receptor Antagonist in Type 2 Diabetes Mellitus. The New England Journal of Medicine; 356:15.

[Rabin R, deCharro F (2001)] EQ-5D: a measure of health status from the EuroQol Group. Annals of Medicine; 33:5.

[So A, DeSmedt T, Revaz S, et al (2007)] A pilot study of IL-1 inhibition by anakinra in acute gout. Arthritis Research & Therapy; 9(2):R28.

[US Department of Health and Human Services, Food and Drug Administration (2008)] Guideline for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Draft Guidance. Docket No HFA-305. Rockville, Md.

[Yki-Jarvinen H, Kauppinen-Makelin M, Tiikainen M, et al (2006)] Insulin glargine or NPH combined with metformin in Type 2 diabetes: the LANMET Study. Diabetologia; 49:442.

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

Appendix 2: Level of TB risk

High risk TB patients are defined as follows:

- HIV positive patients
- Patients on concomitant immunosupressants/ immunodeficiency
- Patients who have been in close contact with active TB
- Chest X-ray suggestive of prior TB infection
- Patients with a history of lack of compliance with anti-tuberculosis drug intake for a prior infection/prophylaxis

Moderate risk TB patients are defined as follows:

- Patients living in or coming from countries with a high prevalence of TB
- Healthcare workers
- Patients with diabetes/ silicosis/ chronic renal failure / malignancies
- Patients exposed to high-risk patients (as described above)
- Infants < 4 years
- Intravenous (i.v.) substance abusers

Low risk TB patients are defined as follows:

- Induration size of 5-9 mm
- None of the risks listed for high and moderate risk patients

Appendix 3: Blood Collection Log for PK, PD and Immunogenicity Samples

Visit	**Pharmacokinetics**			**Pharmacodynamics**		**Immunogenicity**[1]	
Analyte/ purpose	**Canakinumab**			**IL-1β**			
	PK Collection No.	**Sample No.**	**mL**	**Sample No.**	**mL**	**Sample No.**	**mL**
Period II							
Visit 3 (Month 0) Pre-dose[1]	1	1	1	101	1	201	1
Visit 4 (Month 1)	2	2	1	102	1	202	1
Visit 5 (Month 2)	3	3	1	103	1	203	1
Visit 6 (Month 3)	4	4	1	104	1	204	1
Visit 7 (Month 4)	5	5	1	105	1	205	1
Period IV							
Visit 11 (Month 6)	6	6	1	106	1	206	1
Unschedule collection(s)	*7*	*1001*	*1*	*1101*	*1*	*1201*	1
Unschedule collection	*8*	*1002*	*1*	*1102*	*1*	*1202*	1
Unschedule collection(s)	*9*	*1003*	*1*	*1103*	*1*	*1203*	1
Total[3] does not include unschedule collection(s)			6		6		6

[1]All blood samples should be collected prior to the study drug injection.

[2] In case anaphylactoid reactions after injection would occur, two more samples (at the time of the event and 8 weeks later) need to be taken.

[3]Each sample above is taken in duplicate. One sample will be shipped to the Central Lab and one is a back-up sample to remain at the site. Both samples are labeled the same way.