NOVARTIS

Clinical Development

ACZ885/Canakinumab

Clinical Trial Protocol CACZ885T2301 / NCT03447769

A phase III, multicenter, randomized, double blind, placebo-controlled study evaluating the efficacy and safety of canakinumab versus placebo as adjuvant therapy in adult subjects with stages AJCC/UICC v. 8 II-IIIA and IIIB (T>5cm N2) completely resected (R0) non-small cell lung cancer (NSCLC)

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List of abbreviations

ACRped	American College of Rheumatology Pediatric Response Criteria
ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANA	Antinuclear Antibody
ASMA	Anti-Smooth Muscle Antibody
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BLQ	Below limit of quantitation
CAPS	Cryopyrin-Associated Periodic Syndromes
CD-transferrin	Carbohydrate Deficient-transferrin
CHF	Congestive Heart Failure
CMO&PS	Chief Medical Office and Patient Safety
COVID-19	Corona Virus Disease 2019
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	
CT Scan	[redacted] Computerised Tomography Scan
CVD	Cardiovascular Disease
DFS	Disease-free survival
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic Case Report/Record Form
ELISA	Enzyme-Linked Immunosorbent Assay
EORTC	European Organization for Research and Treatment of Cancer Quality of Life
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcomes
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQoL-5 Dimension - % Level
ERCP	Endoscopic Retrograde Cholangiopancreatography

[redacted]

eSAE	Electronic Serious Adverse Event
FAS	Full Analysis Set
FMF	Familial Mediterranean Fever
GGT	Gamma-glutamyltransferase
HA	Health Authority
HAV	Hepatitis A Virus
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
hCG	human chorionic gonadotropin
HEV	Hepatitis E Virus
HGRAC	Human Genetics Resources Administration of China
HIDS	Hyperimmunoglobulin D Syndrome
HR	Hazard Ratio
Hs-CRP	High-sensitivity C-reactive protein
[redacted]	
IA	Interim Analysis
i.v.	intravenous(ly)
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IG	Immunogenicity
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IL-1β	Interleukin-1β
IL-6	Interleukin-6
IMP	Investigational Medical Product
IN	Investigator Notification
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IUD	Intrauterine device
IUS	Intrauterine system
LCSS	Lung cancer specific survival
LFT	Liver Function Tests
LLN	Lower limit of normal
LPLV	Last Patient Last Visit
MACE	Major adverse cardiovascular events
MCV	Mean Corpuscular Volume
mg	Miligram
MI	Myocardial infarction
MKD	Mevalonate Kinase Deficiency
mL	Mililiter
MRI	Magnetic Resonance Imaging
NSCLC	Non-small cell lung cancer

[redacted]

OS	overall survival
PD	Pharmacodynamics
PK	Pharmacokinetics
PHI	Protected Health Information
PPS	Per protocol set
PRO	Patient-Reported Outcome
PT	Prothrombin Time
PTS	Post treatment surveillance
q3w	Every 3 weeks
QFT-PLUS	QuantiFERON®-TB Gold Plus assay
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
R0	Completely resected
RDE	Recommended dose for expansion
REB	Research Ethics Board
RNA	Ribonucleic Acid
R Value	ALT/ALP in x ULN
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
SJIA	Systemic Juvenile Idiopathic Arthritis
SS	Survival Status
SST	Serum Seperating Tube
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1D	Type 1 Diabetes
T3	Triiodothyronine
T4	Thyroxine
TBIL	Total bilirubin
TNF	Tumor Necrosis Factor
TRAPS	Tumor Necrosis Factor Receptor Associated Periodic Syndrome
TSH	Thyroid-Stimulating Hormone
UICC	Union for International Cancer Control
ULN	Upper limit of normal
VES	Visit Evaluation Schedule

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study subject
Control drug	A study treatment 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
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Discontinuation from study	Point/time when the subject permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the subject permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Subject agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 200 mg every 21 days)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care.
Enrollment	Point/time of subject entry into the study; at which informed consent must be obtained. The action of enrolling one or more subjects
Investigational drug/ treatment	Drug whose properties are being tested in the study.
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Subject Number (Subject No. NOVDD) Subject Number (Subject No. NCDS)	A unique identifying number assigned to each subject/subject/healthy volunteer who enrolls in the study
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a subject's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	Is the drug which affects the pharmacokinetics of the other drug
Personal Data	Subject information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization	The process of assigning trial subjects to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized subject

[redacted]

Re-screening	If a subject fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site.
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body.
Stop study participation	Point/time at which the subject came in for a final evaluation visit or when study treatment was discontinued whichever is later.
Study treatment	Any drug or combination of drugs or intervention administered to the study subject as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	Point/time when subject permanently stops taking study treatment for any reason.
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each subject that is required to address the clinical question. The specification of the variable might include whether the subject experiences an intercurrent event.
Withdrawal of consent	Withdrawal of study consent: Withdrawal of consent from the study occurs only when a subject does not want to participate in the study anymore, does not allow any further collection of personal data.

[redacted]

Protocol summary:

Title	A phase III, multicenter, randomized, double blind, placebo-controlled study evaluating the efficacy and safety of canakinumab versus placebo as adjuvant therapy in adult subjects with stages AJCC/UICC v. 8 II-IIIA and IIIB (T>5cm N2) completely resected (R0) non-small cell lung cancer (NSCLC)
Brief title	Study of efficacy and safety of canakinumab as adjuvant therapy in adult subjects with stages AJCC/UICC v. 8 II-IIIA and IIIB (T>5cm N2) completely resected non-small cell lung cancer
Sponsor and Clinical Phase	Novartis, Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This is a multicenter, randomized, double blind, placebo-controlled study evaluating the efficacy and safety of canakinumab versus placebo as adjuvant therapy in adult subjects with stages AJCC/UICC v. 8 II-IIIA and the subset of IIIB with (T>5cm N2 disease) completely resected (R0) non-small cell lung cancer (NSCLC).
Primary Objective(s) and Key Secondary Objective	The primary objective is to compare the Disease-free survival (DFS) in the canakinumab versus placebo arms as determined by local investigator assessment. The key secondary objective is to compare overall survival (OS) in the canakinumab arm versus placebo arm
Secondary Objectives	1. To compare DFS by local investigator assessment and OS in the canakinumab versus placebo arms in subgroups defined by PD-L1 and CD8 expression levels, respectively. 2. To compare lung cancer specific survival in the canakinumab arm versus placebo arm 3. To characterize the safety profile of canakinumab 4. To characterize the pharmacokinetics of canakinumab therapy 5. To characterize the prevalence and incidence of immunogenicity (anti-drug antibodies, ADA) of canakinumab 6. To assess the effect of canakinumab versus placebo on PROs (EORTC QLQ-C30 with QLQ-LC13 incorporated and EQ-5D) including functioning and health-related quality of life
Study design	This phase III, multicenter, randomized, double blind study will evaluate the efficacy and safety of canakinumab as adjuvant therapy in adult subjects with stages AJCC/UICC v. 8 II-IIIA and IIIB (T>5cm N2) completely resected (R0) non-small cell lung cancer (NSCLC). Subjects may be screened after undergoing complete surgical resection of their NSCLC and having R0 status confirmed (negative margins on pathologic review), after completing adjuvant cisplatin-based doublet chemotherapy if applicable, (Radiation therapy is allowed if indicated as per local guidelines or practice). And after all entry criteria are met. Subjects must not have had preoperative neo-adjuvant chemotherapy or radiotherapy to achieve the R0 status. Approximately 1500 subjects will be randomized 1:1 to canakinumab, 200 mg subcutaneously (s.c.) every 3 weeks or matching placebo, s.c., every 3 weeks (Figure 4-1). Randomization will be stratified by AJCC/UICC v. 8 stage: IIA versus IIB versus IIIA versus IIIB with T>5cm, N2 disease; Histology: squamous versus non-squamous; and Region: Western Europe and North America vs. eastern Asia vs. Rest of the world (RoW)
Population	This phase III study will enroll approximately 1500 adult subjects with completely resected (R0) NSCLC AJCC/UICC v. 8 stages II-IIIA and IIIB (T>5 cm N2) disease. These groups have been included to allow all subjects that are able to achieve complete resection of their cancer with negative margins (R0 status). The inclusion of these subjects is consistent with other adjuvant NSCLC studies as they are at a significant risk of relapse to merit inclusion in adjuvant trials. **Applicable for Sub-study (CACZ885T2301A)*:** Will enroll adult subjects with NSCLC Stage IIA-IIIA, IIIB (N2 disease only) who are candidates for complete resection surgery

[redacted]

<table>
<tr><td></td><td>(and therefore prospective candidates for the main study, CACZ885T2301). Biomarker samples pre- and post-surgery will be collected from these subjects.
*For China only: biomarker collection is conditional upon approval from HA, EC and additional authorities (i.e. HGRAC).</td></tr>
<tr><td>Inclusion criteria (applicable for main study)</td><td>1. Written informed consent must be obtained prior to any screening procedures.
2. Age ≥ 18 years
3aCompletely resected (R0) NSCLC AJCC/UICC v. 8 stage IIA- IIIA and IIIB (T>5cm, N2 disease only). Minimal treatments considered adequate prior to study enrollment are:
<table>
<tr><th>Treatment modality</th><th>Minimum extent of treatment required prior to study entry</th></tr>
<tr><td>Surgery</td><td>• Complete surgical resection (R0) is mandatory for all subjects.
• R0 is considered when in microscopic pathology evaluation there are no cancer cells in the surgical margin or within 1mm of the margin.</td></tr>
<tr><td>Chemotherapy</td><td>• Cisplatin-based chemotherapy is mandatory for all subjects (Exception: In subjects with stage IIA disease with no nodal involvement, cisplatin-based chemotherapy can be administered if recommended by the treating physician).
• When required, a minimum of two cycles of cisplatin-based chemotherapy is mandatory, after which additional therapies can be given based upon local clinical practice and/or guidelines.
• Typically, chemotherapy is initiated within 60 days of surgery.</td></tr>
<tr><td>Radiation therapy</td><td>• Radiation therapy is allowed if indicated as per local guidelines or practice.</td></tr>
</table>
The maximum number of days allowed from surgery to randomization is:
• 70 days if subjects were treated with surgery, but did not receive chemotherapy or radiation.
• 182 days if subjects were treated with surgery and chemotherapy, but no radiation.
• 259 days if subjects were treated with surgery, chemotherapy and radiation.
Note:
• Subjects may enter the study earlier than the maximum number of days allowed, if fully recovered from surgery and adjuvant therapies.
• A window of +7 days is allowed to accommodate subject scheduling if needed.
• In case of chemotherapy treatment delays due to toxicities, additional window of +14 days is allowed.
4. Criterion removed.
5. Criterion removed.
6. Criterion removed.
7a. Subjects must have recovered from all toxicities related to prior systemic therapy to grade ≤ 1 (CTCAE v 5.0). Exception to this criterion: subjects with any grade of alopecia, neuropathy (grade ≤2), and subjects meeting the laboratory specifications described in inclusion 8.
8. Subjects must have adequate organ function including the following laboratory values at the screening visit:
• Absolute neutrophil count (ANC) ≥ 1.5 x 109/L
• Platelets ≥ 100 x 109/L</td></tr>
</table>

	• Hemoglobin (Hgb) > 9 g/dL • Creatinine clearance greater than 45 mL/min using Cockcroft-Gault formula • Total bilirubin ≤ 1.5 x ULN • Aspartate transaminase (AST) ≤ 3 x ULN • Alanine transaminase (ALT) ≤ 3 x ULN 9. ECOG performance status (PS) of 0 or 1. 10. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.
Inclusion criteria applicable for sub-study (CACZ885T2301A):	1. Written informed consent to sub-study must be obtained prior to any collections. 2. Age ≥ 18 years 3. Subjects with NSCLC Stage IIA-IIIA, IIIB (T>5cm, N2 disease only) who are candidates for complete resection surgery.
Exclusion criteria (applicable for main study)	1. Subjects with unresectable or metastatic disease, positive microscopic margins on the pathology report, and/or gross disease remaining at the time of surgery. 2. Subjects who received any neoadjuvant treatment. 3a. Presence or history of a malignant disease, other than the resected NSCLC, that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, completely resected carcinoma in situ of any type and hormonal maintenance for breast and prostate cancer >3 years. 4a. History of clinically significant interstitial lung disease (≥grade 2). If radiological changes alone are present at baseline (CTC grade 1 interstitial lung disease) should be added to past medical history/concurrent medical conditions at baseline. 5a. History or current diagnosis of cardiac disease, including any of the following: • recent myocardial infarction or coronary artery bypass graft (CABG) surgery within last 6 months, • uncontrolled congestive heart failure (CHF), • unstable angina (within last 6 months), • clinically significant (symptomatic) cardiac arrhythmias. 6a. Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting cycle 1 day 1 or subjects who have not recovered from radiotherapy-related toxicities. 7. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior to randomization or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and subjects can be enrolled in the study ≥1 week after the procedure. 8. Uncontrolled diabetes as defined by the investigator. 9. Known active or recurrent hepatic disorder including cirrhosis, hepatitis B and C (positive or indeterminate central laboratory results 10a. Subjects must be evaluated for tuberculosis as per local treatment guidelines or clinical practice. Subjects with active tuberculosis are not eligible. In subjects without active tuberculosis, if the results of the evaluation require treatment per local guidelines, then the treatment should be initiated before randomization (unless otherwise required by Health Authorities or Institutional Review Board (IRB) in which case curative treatment must be completed prior to screening) 11a. Subjects with suspected or proven immunocompromised state or infections, including: a. Known history of testing positive for Human Immunodeficiency Virus (HIV) infections. b. Those with any other medical condition such as active infection, treated or untreated, which in the opinion of the investigator places the subject at an unacceptable risk for participation in immunomodulatory therapy. Note: Subjects with localized condition unlikely to lead to a systemic infection (e.g. chronic nail fungal infection) are eligible. c. Allogeneic bone marrow or solid organ transplant

	d. Those requiring systemic or local treatment with any immune modulating agent in doses with systemic effects e.g.: i. Prednisone >20 mg (or equivalent) oral or intravenous daily for >14 days; ii. Prednisone > 5 mg and ≤ 20 mg (or equivalent) daily for > 30 days; iii. Equivalent dose of methotrexate >15 mg weekly. Note: Daily glucocorticoid-replacement for conditions such as adrenal or pituitary insufficiency is allowed. Topical, inhaled or local steroid use in doses that are not considered to cause systemic effects are permitted. Steroids for pre-medication related to chemotherapy as per local standard of care are permitted. 12a. Live or attenuated vaccination within 3 months prior to first dose of study drug (e.g. MMR, Yellow Fever, Rotavirus, Smallpox, etc.). 13. Prior treatment with canakinumab or drugs of a similar mechanism of action (IL-1β inhibitor). 14. History of hypersensitivity to canakinumab or drugs of a similar class. 15. Subjects who have received an investigational drug or device within 30 days prior to first dose of study drug or those who are expected to participate in any other investigational drug or device during the conduct of the study. 16. Subjects who received any biologic drugs targeting the immune system at any time. 17. Any medical condition resulting in a life expectancy of less than 5 years, other than the risk for recurrent lung cancer. 18. Pregnant or nursing 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 19a. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and for up to 3 months after last dose of study drug. Effective contraception methods include: • Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception • Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject • Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/ vaginal suppository • Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. Prior to entry into this study, cisplatin-based chemotherapy, which may be toxic to the fetus, may be given. The time between the end of cisplatin-based chemotherapy and the start canakinumab/placebo treatment is variable, resulting in a variable need for continuation of highly effective contraception. Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks prior to first dose of study drug. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

	No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.
Investigational and reference therapy	All eligible subjects will be randomized in a 1:1 ratio to one of the following two treatment arms: canakinumab 200 mg or matching placebo. The study drug will be given as subcutaneous injections on C1D1 and then every cycle (21 days) for 18 cycles.
Efficacy assessments	Detection of first disease NSCLC recurrence will be done by clinical evaluation that includes physical examination, and radiological tumor measurements as determined by the investigator. In case of non-conclusive radiological evidence, a biopsy should be performed to confirm recurrence. The following assessments are required at screening/baseline: Chest, abdomen and pelvis CT or MRI, brain MRI and whole body bone scan, if clinically indicated. Subsequent imaging assessments will be done every 12 weeks for the first year (treatment phase) following Cycle 1 Day 1, then every 26 weeks during years two and three, and annually during years four and five (post-treatment surveillance phase). The intervals between imaging assessments across all study phases should be respected as described above regardless of whether study treatment is temporarily withheld or permanently discontinued before the last scheduled dose administration on Cycle 18 Day 1, or if unscheduled assessments are performed. If a subject discontinues study treatment for reasons other than recurrence, recurrence assessments should continue as per the scheduled visits until disease recurrence, withdrawal of consent by the subject, subject is lost to follow up, death, or the sponsor terminates the study.
Safety assessments	• Adverse Events (AEs) including Serious AEs (SAEs) • Hematology • Biochemistry • Urinalysis • Coagulation • Pregnancy test (females) • Physical examination • Vital signs • Electrocardiograms (ECG) • Eastern Cooperative Oncology Group (ECOG) performance status
Other assessments	• Blood pharmacokinetics (PK), immunogenicity (IG) and pharmacodynamics (PD) sampling [redacted] • Patient reported outcomes [redacted]
Data analysis	The primary efficacy variable of the study is disease free survival (DFS), defined as the time from the date of randomization to the date of the first documented disease recurrence of NSCLC as assessed by local investigator radiologically or death due to any cause. In case of non-conclusive radiological evidence, a biopsy will be performed to confirm NSCLC recurrence will be used as DFS event and radiological assessment date will be used as DFS event date. DFS events will be assessed locally. The key secondary objective is to determine whether treatment with canakinumab prolongs overall survival (OS) compared with placebo arm. OS is defined as the time from the date of randomization to the date of death due to any cause. If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cut-off date). DFS and OS will also be compared between canakinumab and placebo arms in subgroups defined respectively by PD-L1 and CD8 expression levels. **Pharmacokinetics objectives:** The Pharmacokinetic Analysis Set (PAS) will be used in the pharmacokinetic data analysis. Descriptive statistics (n, m (number of non-zero concentrations), mean, CV%, SD, median, geometric mean, geometric CV%, minimum and maximum) for canakinumab concentrations will be presented at each scheduled timepoint.

[redacted]

	Immunogenicity objectives: Immunogenicity will be characterized descriptively by tabulating anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment. [redacted] **Pharmacodynamics objectives** Descriptive statistics (n, m (number of non-zero concentrations), mean, CV%, SD, median, geometric mean, geometric CV%, minimum and maximum) for total IL-1β concentrations will be presented at each scheduled timepoint. Concentration of total IL-1β vs. time profiles will be displayed graphically. [redacted] **Biomarker objectives*** The analysis of biomarker data [redacted] in the sub-study, will include basic descriptive statistics for all randomized subjects by treatment arm. If on-treatment and post-treatment biomarker data are collected, distribution of change from baseline data will be described. [redacted] the pre- and post-surgery levels of hs-CRP, other cytokines and additional biomarkers in blood from sub-study. All biomarker data will be listed. [redacted] Applicable for the sub-study, the following analyses will be performed: • For all subjects participating into sub-study: to assess the levels of hs-CRP, other cytokines and additional biomarkers in blood at pre- and post-surgery. • For subjects who will also enroll into the main study: to determine whether there is an association between pre- and post-surgery biomarker levels with canakinumab efficacy (e.g. DFS, OS). *For China only: biomarker collection is conditional upon approval from HA, EC and additional authorities (i.e. HGRAC). **Patient Reported Outcomes objectives:** Descriptive statistics will be used to summarize the original scores, as well as change from baseline, of the QLQ-C30/ QLQ-LC13 and EQ-5D-5L at each scheduled assessment time point for each treatment group. Additionally, change from baseline in the scale and subscale values at the time of each assessment will be summarized together with time to first 10 point deterioration and time to 10 point definitive deterioration in symptoms and in global health status/quality of life. Subjects with an evaluable baseline score and at least one evaluable post-baseline score during the treatment period will be included in the change from baseline analyses. **Interim Analysis for Disease Free Survival (DFS)** One interim analysis is planned after approximately 196 of the approximately 392 targeted DFS events (i.e., at approximately 50% information fraction) have been documented. The primary intent of the interim analysis is to stop early for lack of efficacy (futility). There is no intent to carry out an analysis to declare superior efficacy at the time of the interim analysis. **Interim Analyses for Overall Survival (OS)** A maximum of three analyses are planned for OS: the first IA for OS when the final analysis for DFS is performed (provided DFS is statistically significant), when approximately 318 (63%) deaths are expected, the second IA for OS when approximately 418 (83%) deaths are expected, and the final analysis for OS when approximately 504 deaths are expected.
Key words	NSCLC, canakinumab, adjuvant

[redacted]

Amendment 03 (03-Feb-2022)

Amendment rationale

As of 03-Feb-2022, 1840 patients have been screened and 1382 patients have been randomized and treated in the CANOPY A trial. On 23-Apr-2021, the interim analysis of DFS related to futility was performed by independent Data Monitoring Committee (DMC) when 201 DFS events were documented on 01-Feb-2021. The trial was recommended to continue without modification. The last independent DMC review of the safety data from 1234 randomized patients (cut-off date 01-Sep-2021), and the serious adverse events (cut-off date 21-Nov-2021) took place on 12-Dec-2021. The DMC recommendation was that the study can continue without modifications.

The main purpose of this protocol amendment is to:

- Remove the second interim analysis for Disease Free Survival (DFS) originally planned
- Include the comparison between the canakinumab and placebo arms of DFS by investigator local assessment and OS in subgroups defined respectively by PD-L1 and CD8 expression as secondary endpoint.
- Add time to first 10 point deterioration for symptoms and global health status/QoL as a secondary patient-reported outcomes variable of interest
- Add disruption proofing language

Rationale for updating the interim analysis plan for DFS

The originally planned 2nd interim analysis of DFS in this event-driven trial was not performed since the pre-specified number of DFS for this interim analysis (294) had been reached before the planned 1500 subjects were randomized and did not have at least one post-baseline efficacy assessment, which is required by the protocol. As such all the relevant wording in section 4 and 10 are not applicable anymore and have been removed.

As per protocol, the final DFS analysis is planned to be performed when approximately 392 progression events have been observed and all enrolled subjects have a minimal efficacy follow-up of 3 months to ensure all subjects have at least one post-baseline recurrence assessment.

Per sponsor's decision, considering the projected number of DFS events approaching the target for the final DFS analysis the screening activities ended on December 7th, 2021. A total of 1382 subjects were randomized, which is less than 1500 subjects originally planned.

Rationale for including PD-L1 subgroup analysis as a secondary endpoint

PD-L1 expression has shown to be predictive of DFS benefit for adjuvant anti-PD-L1 therapy in the recently reported trial IMpower010 (Felip et al. 2021), which evaluated atezolizumab for the adjuvant treatment of NSCLC. Patients with negative PD-L1 expression (<1%) do not benefit from this therapy, whereas patients with PD-L1 ≥ 1-49% benefit less as shown by DFS HR of 0.87 as compared to 0.43 in PD-L1 ≥ 50% subgroup. Based on those findings, DFS and OS will be compared in the canakinumab versus placebo arms in the PD-L1 subgroups based on ≥1% and ≥50% expression levels.

[redacted]

Rationale for including the evaluation of CD8 expression to identify subjects with an enhanced clinical outcome as a secondary endpoint

An association between CD8+ tumor-infiltrating lymphocytes (TILs) and clinical outcome, including checkpoint inhibitor therapy has been described in NSCLC and various other indications (Fumet et al. 2018, Li et al. 2021). We will evaluate the potential for CD8 expression to identify subjects or subgroups with an enhanced clinical outcome to canakinumab versus placebo.

Rationale to add time to first deterioration for symptoms and global health status/QoL as secondary patient-reported outcomes variable of interest

Time to health-related quality of life (HRQoL) deterioration is a common patient reported analysis conducted in lung cancer trials. Time to first deterioration (not considered definitive) which may be relevant in the adjuvant setting will be explored as a secondary patient-reported outcomes variable of interest to complement the longitudinal HRQoL analysis.

Rationale to remove analysis by per-protocol set (PPS)

Removed PPS set and PPS related sensitivity analysis in line with recommendations from ICH E9 (R1).

Rationale to add disruption proofing language

For inclusion in case of public health emergencies declared by local or regional authorities i.e. pandemic, epidemic or natural disaster. The inclusion of this language follows the latest Novartis protocol template.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

- Section 2.7: a new section for public health emergency mitigation procedures added to align with the latest Novartis protocol template.
- Table 3-1: Added biomarker secondary objectives to compare DFS by local investigator assessment and OS in the canakinumab versus placebo arms in subgroups defined respectively by PD-L1 and CD8 expression levels and time to first 10 point deterioration for symptoms and for global health status/QoL as secondary patient-reported outcomes variable of interest. [redacted] Description of immunogenicity endpoint was updated for clarity. Table reformatted to accomodate new items
- Section 4.2: updated to remove the second interim analysis of DFS; removed the timeline related to it.
- Section 4.3: updated to remove conditional terms associated to the primary DFS analysis
- Section 5.3: re-phrasing of language for exclusion criteria #19
- Section 6.1.1: clarified that study drug should not be administered on the same day or same limb as non-live vaccines in order to distinguish any potential injection related reactions.

[redacted]

- Section 6.3.1: clarified that after a dose missed, subject should resume treatment on the original schedule per C1D1.
- Table 6-2: The table has been updated to correct typos, to add clarity on the recommendations to omit/re-start/discontinue drug, asymptomatic amylase and/or lipase elevation. Reference to CTCAE version updated from "Grade" to "Version"
- Section 6.3.2: central ECG removed as per protocol amendment v01.
- Section 6.3.3.2 updated for clarification regarding potential drug-induced liver injury (DILI)
- Section 6.5.3: Removal of term "efficacy" in relation to interim DFS analysis
- Section 6.6.3.2: clarified that drug accountability can be performed at remote monitoring visit
- Section 7.1: Updated the visit window from ±7 to ±14 days for imaging assessments during years 1-3.
- Section 7.1: added clarification on IMP reconciliation and reference to newly added section 2.7 for public health emergencies. Added clarification that Imaging assessments are to continue regardless of starting a new antineoplastic therapy after discontinuation of study treatment, if the patient has not progressed from their NSCLC or been diagnosed with new lung primary. Clarified that subjects who discontinue from study treatment are to return for the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule.
- Table 7-1: update to record all imaging evaluations in the clinical database. Added definition of SS in footnote
- Section 7.1.4: Rearranged to distinguish discontinuation from study treatment and discontinuation from study.
- Section 7.1.6.2. clarified that Additional survival assessments may be performed outside the 12 weeks follow-up schedules
- Section 7.1.7: Further clarification provided on Lost to follow up procedure
- Section 7.2.1 Visit window updated from ±7 to ±14 days for imaging assessments during years 1-3
- Table 7-3: Visit window of ±7 definition removed for first the first year for consistency with other time periods. Visit windows for imaging assessments defined in Section 7.2.1.
- Section 7.2.2: as part of the latest protocol template, it has been added that safety monitoring of patient's health can be done via phone or virtual call.
- Table 7-5: Updated to include "pancreatic amylase (as needed)".
- Section 7.2.2.6.6: as part of the latest protocol template, it has been added that urine pregnancy test may be done at home.
- Section 7.2.3.1: added clarification that PK/PD/IG will not be collected for subjects that start new antineoplastic therapy after discontinuing study treatment and clarified blood collection volumes. Collection of PK, PD and/or IG samples may be stopped upon decision of the Sponsor under specific circumstances.
- Table 7-6: Cycle 18 row for PK, PD, and IG samples collections removed and a footnote added to provide further clarification
- Section 7.2.3.2: updated analytical method specifications

[redacted]

[redacted]

- Section 8.1.1: Removed duplication of word 'Subject'. Updated available specifications for the category 'outcome'
- Section 8.2.1: Reworded to align with the latest Novartis protocol template. Added that confirmed Corona Virus Disease 2019 (COVID-19) infection should be considered medically significant and reported as SAE
- Section 8.2.2: addition of guidelines on SAE reporting and update of the SUSARs directive.
- Section 8.3: updated to reflect the latest protocol template wording and clarified the patient remains in study follow-up.
- Section 8.4: clarified that in case of a female subject pregnancy, the study treatment should be stopped and the pregnancy consent form read and signed.
- Section 8.4: changed the newborn follow up period from at least 12 months to up to 12 months.
- Section 9.4 updated, patient data report will be issued from EDC and archived.
- Section 10.1.3: removed per-protocol set definition
- Section 10.2: added "in light of COVID-19 pandemic impacting the study during the enrollment phase, demographic and baseline characteristics will be summarized by pandemic phases: pre-pandemic period and pandemic period"
- Section 10.2: removed 'separately' and clarified that relevant medical histories and current medical condition at baseline will be summarized by system organ class and preferred term, by treatment arm
- Section 10.4.1: clarified that disease recurrence includes diagnoses of new primary lung malignancies; clinical deterioration is not considered as a recurrence of disease. In case of non-conclusive radiological evidence, a biopsy assessment will be performed to confirm recurrence; radiological assessment date will be used as DFS event date
- Section 10.4.2: clarified the second interim analysis for DFS was removed
- Section 10.4.3: clarified the subjects receiving anti-neoplastic therapy related to NSCLC willbe censored
- Section 10.4.4: removed DFS analysis by PPS; added sensitivity analysis due to COVID-19 and sensitivity analysis with the subject censored if having two or more times tumor assessments missing; sensitivity analysis without censoring NSCLC related anti-neoplastic therapy
- Section 10.5: added secondary endpoint (DFS and OS in PD-L1 and CD8 subgroups)
- Section 10.5.1: clarified the OS analysis will only be performed when the final DFS analysis is statistically significant
- Section 10.5.2: elaborated secondary endpoint of PD-L1 and CD8 subgroups
- Section 10.5.3.4: clarified the notable ECG values will be summarized by treatment and a listing of these subjects will be produced by treatment arm with notable values flagged

[redacted]

- Section 10.5.3.4: clarified the notable vital sign values will be summarized and a listing of these subjects will be produced by treatment arm with notable values flagged
- Section 10.5.6: time to first 10 point deterioration for symptoms and for global health status/QoL is added together with the definition of the event, analysis and presentation modalities
- Section 10.7.1: Removed the second interim analysis for DFS, revised the boundary values according to EAST 6.4 and modified Table 10-1 with the updated interim plan
- Section 10.7.2: Removed the first interim analysis for OS and DMC responsibility for it; modified Table 10-2 with the updated interim plan
- Section 10.8: Revised sample size calculation for DFS to have only one futility interim analysis for DFS
- Section 10.9: Clarified the power calculation to align with the updated number of analyses for OS
- Section 11.3: as part of the latest protocol template, it has been added that ICF may be collected remotely. Updated ICH GCP to ICH E6 GCP for consistency throughout protocol.
- Section 11.5: Clarified that any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation. Additionally, summary results of primary and secondary endpoints will be disclosed based upon the global Last Patient Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.
- Section 13: New references added
- Appendix 2: addition of stage group IV.

The protocol summary has been updated to reflect the changes throughout the document as well as the list of abbreviations and glossary of terms.

Editorial revisions and text corrections were also included throughout the document.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

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[redacted]

Amendment 02 (05-Feb-2020)

Amendment rationale

As of 05-Feb-2020, 742 patients have been screened and 507 patients have been randomized and treated.

The purpose of the protocol amendment is to allow local laboratory hematology, chemistry, and coagulation to be performed for scheduled safety monitoring visits. Canakinumab has a well-defined safety profile, as outlined in the canakinumab Investigator's Brochure (current Edition 18). Allowing sites the flexibility to perform hematology, chemistry, and coagulation based on local laboratory results allows for same-day safety evaluations. The remaining blood specimens collected as part of safety monitoring (e.g., HIV screen, HbsAg, HCV antibody) will continue to be performed by central laboratory.

Rationale for lipase and amylase grade 2, 3, and 4 update: Definition of grades 2, 3, and 4 lipase and amylase are updated in the dose modification table based on CTCAE v 5.0.

Rationale for increasing window for CT scan after first occurrence of ≥ grade 3 amylase and/or lipase increase: The window for complementary imaging (e.g.CT scan) to assess the pancreas, liver, and gallbladder performed after first occurrence of any ≥ grade 3 amylase and/or lipase is increased to 2 weeks in order to allow for a comprehensive assessment of potential organ injury related to enzyme increase.

Rationale for visit window changes for Post treatment Surveillance, Survival follow up, and Imaging assessments: Visit windows for Survival follow-up visits and Post treatment surveillance visits are increased to +/-7 days in years 2 and 3 in order to harmonize with visit windows for imaging assessments, and +/- 21 days in years 4 and 5 to provide greater flexibility to accommodate the subject's schedule. Imaging assessment windows in years 4 and 5 are increased to ±21 days to provide greater flexibility for the subject's schedule.

Rationale for PK samples reduction (C1D2, C1D3, C6D2, C6D3, C15D1): The PK of canakinumab has been characterized well in other clinical trials. Therefore, additional PK collection at these time points (C1D2, C1D3, C6D2, C6D3, C15D1) is not required as the current number of samples collected is sufficient for representation of those time points. Collection of pre-dose PK sample in cycles, 1, 2, 4, 6, 9, 12 and 18 and samples on day 8 and 15 in cycle 1 is needed for population PK analysis.

Rationale for IG sample reduction (C15D1): The collection of immunogencity sample on C15D1 is removed as the immunogencity of canakimumab has been characterized well in other clinical trials and in this trial. The current immunogenicity samples collected at C15D1 and the immunogencity samples which will continue to be collected at pre-dose on cycles 1, 2, 4, 6, 9, 12, 18 and at end of treatment is considered sufficient to characterize the immunogencity.

Rationale for acceptable alternative brain imaging: MRI with contrast is required but MRI without contrast may be allowed for subjects with contraindication to MRI contrast. Each case will be reviewed and approved by a Novartis study physician.

Rationale for language regarding biomarker collection in China: China requires additional specific review and approval of biomarker samples collections by the HGRAC (Human Genetics Resources Administration of China) other than HA and EC. Therefore for China,

[redacted]

biomarker sample collection [redacted] will not be performed unless approved by HGRAC after the approval from HA and EC.

[redacted]

Rationale for language specifying unblinding with intent to treat with another IL-1β inhibitor: Language specifying unblinding treatment assignment with the intent to treat with another IL-1β inhibitor is included to specify that approval by a Novartis physician is required in this case. This is to mitigate any unintended unblinding as the subject could potentially enroll into another Novartis clinical trial.

Rationale for language regarding data collection of race and ethnicity: The clarification that participant race and ethnicity are collected to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities, in accordance with General Data Protection Regulation requirements.

Additional minor protocol language clarification updates are made throughout the amendment.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

List of changes to protocol:

- Protocol Summary, Section 2.2, Table 3-1, Table 3-2, Table 7-1, Table 7-2, Table 7-5, Table 7-7, Section 7.2.4.2: For China only: biomarker collection is conditional upon approval from HA, EC and additional authorities (i.e. HGRAC).
- Protocol Summary, Section 5.2:
  - Update to inclusion criterion 3a to clarify that adjuvant chemotherapy is not mandatory for stage IIA, but may be done if the treating physician recommends chemotherapy. Also clarified that a minimum of two cycles of cisplatin-based chemotherapy is mandatory when adjuvant chemotherapy is required.
- Protocol Summary, Section 5.3:
  - Update to exclusion criterion 2 to clarify that any neoadjuvant treatment is excluded.
  - Update to exclusion criterion 12a to clarify that live or attenuated vaccines are excluded.
  - Update to exclusion criterion 16 to clarify subjects who received any biologic drugs targeting the immune system at any time are excluded.
- Section 2.2, Section 5.1, Section 5.2, Section 5.2.1, Section 7.1.2: Update of stage IIIB description to "T>5cm, N2" for consistency throughout the protocol.
- Table 6-2:
  - Lipase/Amylase grade 2, 3, and 4 definitions are updated based on CTCAE v5.0.

[redacted]

  - Window for CT scan or other imaging study to assess the pancreas, liver, and gallbladder after the first occurrence of any ≥ Grade 3 of amylase and/or lipase is increased to 2 weeks.
  - Footnotes are removed from the bottom of the table and added directly to the relevant sections.
- Section 6.4.2.1: Clarified that live or attenuated vaccines are prohibited.
- Section 7.1, Section 7.1.3: Visit windows for post-treatment surveillance and survival follow-up are increased to ±7 days in years 2 and 3, and ±21 days in years 4 and 5.
- Section 7.1, Section 7.1.3, Section 7.2.1: Imaging assessment visit windows are increased to ±21 days in years 4 and 5.
- Table 7-1:
  - Updated the VES to clarify that Cycle 18 and EOT are the same visit.
  - C1D2 and C1D3 are removed from the VES table.
  - [redacted]
  - Removed "Category" column and added directly to the table "X" to indicate assessment to be recorded in the clinical database or received electronically from a vendor, or "S" to indicate assessment to be recorded in the source documentation only.
- Table 7-1, Table 7-6: Removed the following PK collection visits: Cycle 1 Day 2, Cycle 1 Day 3, Cycle 6 Day 2, Cycle 6 Day 3, Cycle 15 Day 1. Removed IG sample collection at Cycle 15 Day 1.
- Table 7-2: Added footnote "X" to indicate assessment to be recorded in the clinical database or received electronically from a vendor.
- Section 7.1.6.1, Section 8.1.1, Section 8.2.2: Clarified if a new antineoplastic therapy is initiated after discontinuation of study treatment, only SAEs (and not AEs) suspected to be related to study treatment will be collected in the Adverse Events eCRF.
- Section 7.2.1: Removed brain CT and updated that MRI without contrast is acceptable for brain imaging assessment.
- Section 7.2.2.6: Clarified that hematology, chemistry, and coagulation evaluations may be performed locally for scheduled safety visits.
- Table 7-5: Updated table title to "Clinical laboratory parameters collection plan." Removed asterisk explaining that "fasting glucose" would be collected in a fasting state.
- Section 7.2.2.6.4: Removed sentence "if the coagulation blood samples collected at screening is clotted when received by central laboratory for testing or the central laboratory results of only the coagulation are delayed, the subject is still eligible to enter the study with a local laboratory INR test ≤1.5."
- Section 7.2.2.6.6: Included "total hysterectomy" as not of child bearing potential.
- Section 7.2.3.1: Update of centrifuge speed for serum PK and IG samples to 2500 g.
- [redacted]

[redacted]

- Section 8.1.3: Updated to replace the Adverse Event of Special Interest (AESI) name 'Hepatic transaminases and bilirubin elevations' with the new AESI name 'Abnormal Liver Parameters'.
- Section 8.3: Included language for emergency unblinding for consideration of subsequent treatment with an IL-1β inhibitor.
- Section 8.4: Updated to clarify that if a subject becomes pregnant while on study treatment, the newborn will be followed for at least 12 months.
- Section 10.2: Clarification that participant race and ethnicity are collected to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

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[redacted]

Amendment 01 (11-Dec-2018)

Amendment rationale

As of 11 December 2018, 105 subjects have been screened to the study. 63 subjects have been randomized and treated.

The main purpose of this protocol amendment is to:

1. Include a biomarker sub-study which collects pre- and post- resection surgery blood samples.
2. Central ECG collection will be replaced by local ECG at screening and as clinically indicated.
3. Update dose interruption schedule related to Drug Induced Liver Injury (DILI).
4. Update the contraception language.
5. Reduce number of C1D2 and C1D3 pharmacokinetics samples.
6. Make clarifications, editorial and typographic changes.

Rationale for including biomarker sub-study (CACZ885T2301A):

The sub-study will be identified as CACZ885T2301A. Biomarker samples will be collected to understand how resection surgery may impact hs-CRP, other cytokines and additional biomarker levels in blood. This will be assessed based upon the following two objectives:

- To assess the levels of hs-CRP, other cytokines and additional biomarker levels in blood at pre- and post- surgery.
- To determine whether there is an association between pre- and post-surgery biomarker levels with canakinumab efficacy (e.g. DFS, OS).

Rationale for central ECG removal: Canakinumab is IgG-type antibody with a large molecular size that displays no evidence of drug-related changes to electrocardiogram (ECG). Moreover, no clinical signs or qualitative or quantitative electrocardiographic changes attributable to canakinumab administration were observed in the toxicology studies performed. In addition, no abnormal binding to cardiac or cardiovascular tissues was identified in any of the cross reactivity studies using marmoset and human tissues. QT prolongation and Cardiotoxicity is not considered a safety concern for canakinumab and it is not included in the Risk Management Plan (RMP) as identified or potential risk. In CANTOS study, QT prolongation AEs were reported 23, 26 and 27 subjects (1%; 1.1% and 1.2%) in the canakinumab 300mg; 150mg and 50mg arm respectively, while 46 subjects (1.4%) experienced QT prolongation AEs in the placebo arm. Based upon above data, ECG collection is not required to be collected centrally and can be performed locally once at screening and on study if clinically indicated.

Rationale for updating the dose interruption schedule related to Drug Induced Liver Injury (DILI): Sections to Table 6-2 has been updated include the new DILI language and the dose modification table for hepatotoxicity was updated based on the updated Novartis Hepatotoxicity Clinical Safety Guideline (2018).

[redacted]

Rationale for revising contraception language: In an embryo-fetal development study in marmosets canakinumab showed no maternal toxicity, embryo-toxicity or teratogenicity when administered throughout organogenesis. In addition, canakinumab did not elicit adverse effects on fetal or neonatal growth when administered throughout late gestation, delivery and nursing. Based on this data, the protocol is being updated to require basic contraception (from highly) for women of childbearing potential treated with canakinumab monotherapy as per the Novartis standards. The duration of contraception after discontinuation of the study drug was amended from 130 days to 3 months after last dose in line with the canakinumab IB and EuSmPC.

Rationale for reducing PK samples at C1D2 and C1D3: The C1D2 and C1D3 PK time points will be reduced and only a subset of approximately 400 subjects will have these time points taken. Collection of these post-dose PK samples during the absorption phase is needed to allow population PK analysis in the targeted population. This will be adequate to capture the absorption profile and derive the associated absorption parameters after SC injection of canakinumab.

Additional summary of changes:

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Section	Brief description of the change and/or new text
List of abbreviations	Updates made to list of abbreviations.
Glossary of terms	Updated to include the updated definitions.
Protocol summary	Protocol summary sections have been updated to match the body of the protocol.
Section 1.3.1.2.1	This section is to provide information on clinical experience. Therefore, texts providing instructions to Investigators has been moved to the Adverse event of special interest (AESI) Section 8.1.3.
Section 2.2	Table 2-2 was removed as it did not provide the full AJCC/UICC v 8 staging guidelines. Additionally, text was updated to include specifications for sub-study.
Section 3	Minor changes have been made to Table 3-1 to clarify wording on endpoints. Table 3-2 containing sub-study objectives" has been included.
Section 4.1	Updated to provide information on the sub-study study design, including Figure 4-2.
Section 5.1	Redundant text has been removed. Table 5-1 has been removed as it did not include the full scope of staging guidelines. Inclusion criteria has been revised to clarify what is the minimum requirement to enter study. Description on sub-study population was also added.
Section 5.2	Inclusion criteria 3, 4, 5, 6 (now 3a) have been revised into one to provide clarity.
Section 5.2	Inclusion criteria 5 (now 5a) has been updated to indicate CTCAE v 5.0 will be used and added clarification text.
Section 5.2.1	Inclusion criteria 1, 2, 3 for the sub-study has been created.
Section 5.3	Exclusion criteria 3, 4, 5, 6, 10, 11, and 12 have been revised to provide more clarification. Revised criterions has letter “a” added.

[redacted]

Section 5.3	Exclusion criteria 19 has been revised to reflect the requirements of basic methods of contraception and continued use of contraception for up to 3 months after last dose of study drug. Add in language to clarify that it is bilateral tubal ligation.
Section 6.1.5, Section 7.1, Section 7.1.3, Section 7.1.4, Section 7.1.6.1, Section 7.2.1, and Section 8.1.1	These sections have been updated to include guidance on what must be done upon start of new antineoplastic therapy.
Section 6.3.3.2 and Table 6-2	Has been updated to include the new DILI language and the dose modification table for hepatotoxicity was updated based on the updated Novartis Hepatotoxicity Clinical Safety Guideline (2018).
Section 6.4	Text updated to provide clarity on types of virus excluded. Added ‘supplements.Drug-drug Interaction language not applicable for adjuvant setting has been removed.
Section 6.4.2.1	Further information on examples for immune modulating agent in doses with systemic effects has been included.
Section 6.4.2.2	Other anticancer therapy section has been included to provide further clarity to the protocol.
Section 6.5.1	Updated to include subject number for sub-study.
Section 6.6 and Section 14.1	Study drug preparation has been revised to be in line with the latest instructions.
Section 7.1	Table 7-1 has been updated to include corrections including: Disease recurrence was clarified to specify that it is referring to NSCLC recurrence. Visit numbers have been corrected. Missing IG time points were added. PK time points revised. Updates/corrections have been made to the protocol section numbering, time points for the following has been updated: Whole body bone scan, ECG and Adverse events. Table 7-2 has been added to list all of the assessments to be performed for the sub-study. Footer has been clarified to specify the number of subjects that will need to provide samples for Cycle 1 Day 2, Cycle 1 Day 3, Cycle 6 Day 2, and Cycle 6 Day 3.
Section 7.1.2	Re-screening information has been added. Updated to include information on the screening procedures to be performed for sub-study participants. Details related to sub-study participants have been added.
Section 7.1.2.2	Information to be collected on screen failure subjects has been updated.
Section 7.1.2.4	Added in section to clarify the information to be collected on sub-study participants
Section 7.1.4	Details on discontinuation process has been clarified.
Section 7.1.5	Withdrawal of consent language has been updated to include the GDPR requirements.
Section 7.2.1	Recurrence assessment has been clarified and allowance of Brain CT has been included.
Section 7.2.2.1	Tuberculosis language has been simplified.
Section 7.2.2.6	Table 7-5 was updated to include missing tests.
Section 7.2.2.6.6	Updated to specify that it is bilateral tubal ligation and at least six weeks prior to first dose of study drug. Removed sentence referring to male subjects notifying investigator or partner pregnancy. This applicable for this study.
Section 7.2.2.7.1, and Section 9.3	Sections have been revised as central ECG collection is not needed. Language has been updated to include one collection at screen and as clinically indicated for local ECG collection.

[redacted]

Section 7.2.3.1	PK and PD sample handling has been revised. Table 7-6 has been revised to reduce PK sampling at Cycle 1 Day 2 and Cycle 1 Day 3. The Dose ID numbering has been corrected and IL-1β sample number has been added. The foot note has been clarified.
Section 7.2.4.1	The minimum number of slides required has been revised in the Biomarker sample collection plan.
Section 7.2.4.2	Biomarker sub-study section has been included.
Section 7.2.6.2	Removed sentence stating investigator has to review ePROs for potential AEs or SAEs as this is not required.
Section 8.1.1	Sentence regarding malignancy has been removed and updated language has been added to section 8.2.2.
Section 8.1.3	Examples of AESI has been updated. Text on infections and neutropenia was added to this section from Section 1.3.1.2.1.
Section 8.2.2	Details on SAE reporting has been included for instances of NSCLC recurrence, new primary lung cancer and new primary malignancy in organs other than lung. SAE reporting items applicable to sub-study has been added.
Section 8.6	Revised the DMC safety review time points.
Section 10.4.1 and section 10.4.4	In these sections and throughout the document, disease recurrence was clarified to specify that it is referring to NSCLC recurrence.
Section 10.4.2	Clarified the time points at which DFS estimates will be summarized.
Section 10.5.3.3 and throughout the document	CTCAE version has been updated to 5.0
Section 10.5.3.4	Clarified the planned ECG analysis in reflection of changes to ECG related collection.
[redacted]	
Section 10.5.6	Clarified the event occurrence for time definitive deterioration.
Section 10.6.1	Added analysis details for sub-study.
Section 10.7.2	Footnote for Table 10-2 has been revised to clarify that OS will be tested only if either 2nd interim or the final DFS analysis is significant.
Section 10.10	Sample size consideration in the sub-study has been added.

IRB/IEC

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[redacted]

1 Background

1.1 Clarification statement regarding staging system used to assess subject eligibility in this study

Please note that, unlike publications referenced in this protocol, inclusion and exclusion criteria are based on the new IASLC staging system (AJCC v.8) (AJCC Cancer Staging Manual). The complete list of changes from prior American Joint Committee on Cancer (AJCC) v.7 to AJCC v.8 are summarized by Goldstraw et al (2016) and include the following, which are important for eligibility purpose: Stage IB subjects with T>4-5cm become Stage IIA; Stage IIIA subjects with T>5cm N2 become stage IIIB. Both groups are eligible for this study if completely resected with negative margins (see Section 5 for complete list of inclusion/exclusion criteria). The inclusion of these subjects is consistent with other adjuvant NSCLC studies as they are at a significant risk of relapse to merit inclusion in adjuvant trials.

1.2 Overview of disease pathogenesis, epidemiology and current treatment

An estimated 1.8 million people were diagnosed globally with lung cancer in 2012 and there were 1.6 million deaths from this disease (Globocan 2012). Non-small cell lung cancer (NSCLC) accounts for 85% of the lung cancer diagnoses (Jemal 2011). The majority of subjects present with advanced disease; only 25-30% of subjects have surgically resectable disease and only half of these resected subjects are disease-free at 5 years (ACS 2012-2013). Meta-analysis of five large adjuvant cisplatin based chemotherapy versus observation trials demonstrated an absolute improvement in 5-year survival of 5.4% in subjects with resected stages IB through IIIA (Pignon 2008). Subjects with stage IB disease and large tumors demonstrated a trend toward benefit from adjuvant chemotherapy with a survival HR=0.93 (not statistically significant), whereas, subjects with stages II-III had a statistically significant improvement in survival with HR=0.83 (Pignon 2008). The standard of care for stages IIA-IIIA is entire surgical resection (margins free of cancer), followed by 4 cycles of cisplatin based chemotherapy (NCCN guideline July 2017). Radiation therapy is suggested in addition to chemotherapy for subjects with IIIA N2 disease (NCCN guideline July 2017). Despite adjuvant chemotherapy, only approximately 60% of subjects with stage IB disease will be alive at 5 years, only approximately 50% of stage II subjects and only approximately 40% of subjects with stage IIIA diseases will be alive at 5 years (Douillard et al 2006). Thus, new adjuvant therapies continue to be urgently needed to improve the disease-free and overall survival of NSCLC subjects.

Recently, a new IASLC staging system has been published which harmonizes AJCC and UICC staging systems to ensure subjects with similar prognosis are regrouped within the same stage category. The changes are summarized by (Goldstraw 2016). As an example, subjects with stage IB per AJCC v.7 have a 5 year overall survival of 71% (Goldstraw 2016). Those subjects with stage IB with primary tumors of >4-5cm have a 5 year survival of 66% are more similar to the IIA N0 who have primary tumors of >5-6 cm, who have a 63% 5-year survival; therefore these prior IB subjects are now moved to stage IIA in the new AJCC and UICC harmonized version 8 staging system. The AJCC v. 7 stage IB subjects have a 5 year OS of 71% now in AJCC v. 8 have a 73% 5 year OS. Similarly, subjects with AJCC v. 7 Stage IIIA N2 disease become stage IIIB with T>5 cm N2 disease in the new IASLC system.

[redacted]

Chronic inflammation plays an important role in the development of non-small cell lung cancer (NSCLC). Key etiological risk factors such as smoking, second-hand smoke exposure, chronic infections such as tuberculosis, and exposure to environmental toxins such as asbestos, silica dust, and various metal dusts cause a chronic inflammatory milieu that plays a critical role in carcinogenesis, particularly, in lung cancer (O'Callaghan 2010, Krysan 2008). Indeed, elevation of the general inflammatory marker high-sensitivity C-reactive protein (hs-CRP) is associated with an increased risk of developing lung cancer (Chaturvedi 2010). It is also well established that smoking, a lung cancer risk factor, induces chronic pulmonary inflammation and this inflammation is thought to be one of the mechanisms that drive tumor promotion (Bracke 2006). Finally, there is also evidence that anti-inflammatory drugs can reduce the risk of lung cancer development. In a meta-analysis of lung cancer studies, Khuder et al. demonstrated a 21% relative risk reduction in the development of lung cancer for those subjects reporting nonsteroidal anti-inflammatory drug (NSAID) use (Khuder 2005). Taken together, these observations suggest an important role for inflammation in the development of lung cancer.

The cytokine interleukin-1β (IL-1β) is thought to be one of the mediators of pulmonary inflammation that promotes lung cancer. Genetic evidence also links IL-1β to lung cancer risk. Polymorphisms in the promoter region of the IL-1 gene result in altered levels of IL-1β expression and are associated with an increase in lung cancer risk (Li 2013). In addition to this clinical data, there is extensive preclinical data to support the role of IL-1β in several distinct steps in carcinogenesis. These steps include tumor initiation, promotion, angiogenesis, and metastasis (Dalgleish 2006, Mantovani 2008, O'Byrne 2000, O'Byrne 2001). Tumor initiation is the first step in carcinogenesis and involves the acquisition of mutations in normal cells that allow a selective growth advantage. IL-1β is thought to create a microenvironment that promotes tumor initiation (Wu 2016). In a mouse model of tumor initiation, the genetic loss of IL-1β resulted in an attenuation of 3-MCA-induced tumor formation (Krelin 2007, Voronov 2010). The ability of IL-1β to promote tumor initiation is thought to be mediated through the induction of NF-κB expression (Kasza 2013). The second step in carcinogenesis is tumor promotion. This step is characterized by the growth of a primary tumor from a single transformed cell. This step is mediated in part by tumor associated macrophages (TAM) and cytokines that these TAMs produce, such as TNFα, IL-6, and IL-1β (Becker 2006). The third step in carcinogenesis is angiogenesis, in which blood vessel formation is induced to generate a vascular network for the primary tumor. In this process, IL-1β is thought to play a critical role, as tumors in mice deficient in IL-1β failed to induce vascular endothelial growth factor (VEGF) expression and tumor angiogenesis (Apte 2006). The final step in carcinogenesis is metastasis. IL-1β is thought to play an important role in this step as well via the induction of genes critical for invasion and cell adhesion. Using a mouse model of lung cancer metastasis, Yano and colleagues demonstrated that tumors genetically programed to express high levels of IL-1β developed lung metastasis more rapidly than controls, while treatment with an anti-IL-1β antibody inhibited formation of lung metastasis (Yano 2003). Taken together, these results suggest an important role for IL-1β in multiple steps of carcinogenesis.

Given the evidence for the importance of IL-1β signaling in carcinogenesis, some in the scientific community have already proposed to treat cancer with IL-1β blockade (Jenkins 2017, Wu 2016). Lung cancer is the largest cause of cancer deaths on the globe. In 2015, lung cancer was responsible for 1.68 million deaths (WHO Cancer FACT Sheet Feb 2017). Despite adjuvant

[redacted]

chemotherapy, only approximately 60% of subjects with stage IB disease will be alive at 5 years, only approximately 50% of stage II subjects and only approximately 40% of subjects with stage IIIA diseases will be alive at 5 years (Douillard et al 2006). Thus, treatments to improve the survival of subjects resected for cure are urgently needed.

1.3 Introduction to investigational treatment(s) and other study treatment(s)

1.3.1 Overview of canakinumab

Canakinumab is a high-affinity human anti-Interleukin-1β (IL-1β) monoclonal antibody that belongs to the IgG1/κ isotype subclass. The relative molecular mass of canakinumab based on the amino acid sequence without post-translational modification (e.g., glycosylation), but including N-terminal pyroglutamate formation and the C-terminal lysine residues at the heavy chains, is MW = 145157 Da. Canakinumab is manufactured in a murine SP2/0 cell line.

Table 1-1 Canakinumab characteristics

Chemical name:	Recombinant human monoclonal antibody ACZ885
INN:	Canakinumab
Proprietary name:	ILARIS®
Drug class:	Anti-inflammatory
Laboratory code:	ACZ885

1.3.1.1 Non-clinical experience

1.3.1.1.1 Non- clinical pharmacokinetics and metabolism

Canakinumab exhibits typical immunoglobulin G (IgG) kinetics with a limited volume of distribution, a slow clearance and a long terminal half-life. The bioavailability of canakinumab estimated after single subcutaneous (s.c.) dose administration was 60% using cross-study comparison of exposure between intravenous (i.v.) and s.c. routes of administration. Exposure to canakinumab was linear and dose proportional within the dose range investigated in marmoset.

For further details, please refer to Section 4.2 of the current [canakinumab Investigator's Brochure].

1.3.1.1.2 Non clinical pharmacology

Canakinumab neutralizes the bioactivity of human IL-1β by preventing its binding to the IL-1β receptor. Canakinumab specifically binds human IL-1β with a Kd of 40-60 picomolar and has no cross-reactivity with human IL-1α (IL-1F1), human IL-1 receptor antagonist (IL-1Ra, IL-1F3) or other members of the IL-1 family (IL-1F4-IL-1F9). Canakinumab is selective for human and marmoset IL-1β (IL-1F2) but does not bind to mouse, rat, rabbit, rhesus nor cynomolgus monkey IL-1β. Because canakinumab does not react with rodent IL-1β, the *in vivo* activity of canakinumab was demonstrated in models on inflammation induced by human IL-1β in rodents. Canakinumab inhibited the IL-1β induced effect. For further details, please refer to the current [canakinumab Investigator's Brochure].

[redacted]

1.3.1.1.3 Toxicology

An extensive program of toxicology studies was performed. The marmoset monkey was characterized as an appropriate model to predict human safety. Regarding toxicokinetics, exposure to canakinumab was demonstrated. Following i.v. or s.c. administration, canakinumab was well tolerated in marmosets at all dose levels investigated without any relevant adverse findings. No anti-drug antibodies were detected. Long-term animal studies have not been performed to evaluate the carcinogenic potential of canakinumab. The mutagenic potential of canakinumab was not evaluated. No significant treatment-related effects were observed with respect to male or female fertility in a mouse model using a murine analog of canakinumab. For further details, please refer to the current [canakinumab Investigator's Brochure].

1.3.1.2 Clinical experience

Seventy-four (74) Novartis-sponsored canakinumab studies (66 interventional studies, 5 integrated managed subject access programs, and 3 post-authorization safety studies) and 16 Third Party (Investigator Initiated) trials had been initiated by 30-Jun-2017. A total of 15,902 subjects had been enrolled in the Novartis-sponsored, interventional canakinumab studies. It is estimated that 10,939 subjects were exposed to canakinumab treatment in these trials, with the majority of subjects (6,717) being enrolled in the pivotal CACZ885M2301 study (Canakinumab ANti-inflammatory Thrombosis Outcomes Study, CANTOS) investigating the prevention of recurrent cardiovascular events in subjects with a prior myocardial infarction (MI) and an elevated hs-CRP. It is additionally estimated that 528 unique pediatric subjects aged <1 to 17 years were exposed to canakinumab treatment in Novartis-sponsored interventional studies [canakinumab Investigator's Brochure].

The safety, tolerability and efficacy data of canakinumab in completed Novartis-sponsored interventional studies (studies with a clinical study report as of 30-Jun-2017) are available from 3,861 male or female subjects exposed to the drug; these include 326 healthy subjects, 458 subjects with Cryopyrin-Associated Periodic Syndromes (CAPS), 324 with Systemic Juvenile Idiopathic Arthritis (SJIA), 441 with Rheumatoid Arthritis (RA), 1,179 with gouty arthritis, 95 with respiratory indications, 673 with Type 2 Diabetes Mellitus (T2DM), 144 with cardiovascular indications, e.g. atherosclerosis and periphery artery disease, 64 with osteoarthritis and 157 with other indications. The doses administered ranged from 0.5 mg/kg to 9 mg/kg s.c., 0.03 mg/kg to 10 mg/kg i.v., and fixed doses of 5 mg to 600 mg s.c. and 150 mg to 600 mg i.v. The frequency of dosing ranged from a single dose to quarterly repeated administration or treatment upon flare (in gouty arthritis) [canakinumab Investigator's Brochure].

1.3.1.2.1 Clinical Safety

Due to the mode of action of all inhibitors of the IL-1 pathway, infections, predominately of the upper respiratory system, are the main risk in subjects treated with canakinumab. Canakinumab is associated with an increased incidence of serious infections during and after treatment. Although the majority of reports of infection resolved spontaneously or with standard therapy, severe, serious and fatal infections have been reported, including reports of fatal complicated perforated diverticulitis and sepsis. Opportunistic infections have also been reported.

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Neutropenia has been observed with medicinal products that inhibit IL-1, including canakinumab. Other than neutropenia, thrombocytopenia, and uric acid increase specific for active gouty arthritis, there was no evidence of other clinically relevant drug-related changes in vital signs, electrocardiogram (ECG) or laboratory values (see local label for Ilaris®).

Both *i.v.* and *s.c.* injections of canakinumab are well tolerated as evidenced by a low rate of injection-site events and discontinuations. Low treatment-related immunogenicity (<3%) has been detected, and no clinical consequences to detected anti-drug antibodies were evident. No apparent impact on canakinumab pharmacokinetics or on total IL-1β concentration (pharmacodynamics) were evident; or any evidence of immune-related loss of efficacy. Overall, the immunogenicity profile is entirely consistent a cross all disease areas.

1.3.1.2.2 Clinical Efficacy

Canakinumab has demonstrated efficacy in a variety of non-oncologic indications.

In CAPS subjects, the first approved indication of canakinumab, canakinumab treatment (150 mg or 2 mg/kg *s.c.* every 8 weeks) produces a rapid and complete resolution of signs and symptoms in almost all subjects, starting within 1 day of treatment, along with an immediate and sustained normalization of serological and hematological parameters of inflammation. Pediatric subjects and those with a severe CAPS phenotype may require higher than usual doses to attain full clinical response and current labeling for Ilaris allows for dose escalation to 8 mg/kg for subjects ≤ 40 kg and to 600 mg for subjects > 40 kg.

Significant improvement in disease activity was demonstrated in subjects with period fever syndromes including Familial Mediterranean Fever (FMF), Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) and Hyperimmunoglobulin D Syndrome (HIDS)/ Mevalonate Kinase Deficiency (MKD) who had received canakinumab treatment (150 mg every 4 weeks). Canakinumab treatment showed resolution of index disease flare and prevention of new flares. Canakinumab also demonstrated normalization of serological and hematological parameters of inflammation. Subjects with HIDS/MKD may require higher than usual doses to attain full clinical response. The response to treatment was long-lasting and sustained in all evaluated age-groups, both genders, and between all indications.

In SJIA, subjects treated with a single dose of canakinumab (300 mg or 4 mg/kg), 83% of all children were classified responders and achieved at least an adapted American College of Rheumatology Pediatric Response Criteria score of ACRped30 at Day 15 of a 4-week randomized double-blind study. One third of subjects achieved an ACRped100.

In subjects with gouty arthritis who had an acute gout attack and who are refractory or contraindicated to NSAIDs and/or colchicine, treatment with canakinumab (150 mg *s.c.*), showed statistically significant efficacy, both in terms of pain relief and preventing the onset of a new flare, compared to triamcinolone acetonide 40 mg intramuscularly (*i.m.*). In confirmatory gout studies, canakinumab has showed sustained efficacy with a consistent safety profile over repeated treatment.

In subjects with atherosclerosis and Type II Diabetes Mellitus or Impaired Glucose Tolerance, the rate of progression of atherosclerotic plaque burden (as measured by vessel wall area) in three vascular beds (proximal ascending aorta, left carotid, right carotid) was attenuated after 12 months of treatment with canakinumab.

[redacted]

In subjects with intermittent claudication, an improvement in maximum and pain-free walk distance in the canakinumab-treated group was observed, but no statistically significant between-treatment difference in mean vessel wall area ratio was determined as compared to baseline.

For further details, please refer to the [canakinumab Investigator's Brochure].

Efficacy in the CANTOS study

The CANTOS study has demonstrated a clinically and statistically significant effect of canakinumab 150 mg and 300 mg every 3 months over matching placebo in reducing the risk of major adverse cardiovascular events (MACE), a composite endpoint of cardiovascular death, non-fatal MI and non-fatal stroke in subjects with a history of MI and inflammatory atherosclerosis. With the positive results of the CANTOS study, canakinumab is the first treatment to significantly reduce cardiovascular risk by directly targeting inflammation. The results of the CANTOS study also recently reported that inhibition of IL-1β dose dependently reduced the occurrence of lung cancers in post myocardial infarction (atherosclerotic) subjects with elevated hs-CRP, who were previously cancer free (see Section 2.1).

1.3.1.2.3 Clinical Pharmacokinetics, Pharmacodynamics and Immunogenicity

Canakinumab is a human anti-human IL-1β monoclonal IgG1/κ antibody which was derived from a genetically engineered mouse carrying the human immunoglobulin repertoire. During the development of canakinumab, three changes relevant to drug substance manufacturing process were introduced. The four drug forms were termed as Product Types A, B, C and D. The rate and extent of absorption following s.c. administration were independently estimated for the four product types for the CAPS extension registration dossier. Bioavailabilities and absorption rate constants of the product types were similar, ranging from 63 to 76 % and 0.28 to 0.38 day^{-1}, respectively. The bioavailability assessments of product types C and D (marketed product) were 76% and 66%, respectively. Based on the relative bioavailability of D/C of 0.87 ± 0.11 (mean ± SEM), it was concluded that there was no apparent difference in the two product types. Two different formulations of canakinumab have been administered during its development: a lyophilized powder form and a solution for injection formulation. A bioequivalence study, CACZ885A2104, demonstrated the bioequivalence of the lyophilized form of canakinumab and the canakinumab solution for injection in a pre-filled syringe, one of the presentations of the liquid formulation. Other presentations of the liquid formulation include an auto-injector and the liquid in a vial. Study CACZ885M2101 demonstrated bioequivalence of canakinumab in a liquid formulation administered via auto-injector or pre-filled syringe. No difference in bioavailability of the solution in a vial compared to powder for solution for injection was detected in a population PK analysis of PK data from Study CACZ885N2301.

The peak serum canakinumab concentration (C_{max}) occurred approximately 7 days following single s.c. administration of 150 mg in adult CAPS subjects. Based on a population PK analysis in the CAPS population including children from 2 years of age, the absolute bioavailability of s.c. administration of canakinumab was estimated to be 66 %. Exposure parameters (such as AUC and C_{max}) increased in proportion to dose over the dose range of 0.30 to 10.0 mg/kg given as i.v. infusion or from 150 to 600 mg as s.c. injection.

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The serum clearance (CL) and volume of distribution of canakinumab varied according to body weight (6.01 L and 0.174 L/day in a typical CAPS subject weighting 70 kg). The mean terminal half-life was 26 days. After accounting for body weight differences, no clinically significant differences in the PK properties of canakinumab were observed between CAPS, TRAPS, HIDS/MKD, FMF, SJIA and gouty arthritis subjects. There was no indication of accelerated clearance or time-dependent change in the PK properties of canakinumab following repeated administration.

Canakinumab binds to human IL-1β, and blocks the interaction of this cytokine with its receptors, thereby functionally neutralizing its bioactivity. The resulting complex of canakinumab and IL-1β is eliminated at a much slower rate than the free IL-1β, resulting in elevation of total IL-1β (free plus complex) following canakinumab administration. Thus, measurement of free plus complexed IL-1β, i.e. total IL-1β, is a relevant PD biomarker for canakinumab indicative of binding of IL-1β by the antibody. An increase in total IL-1β was observed in both healthy subjects as well as subject populations, after canakinumab dosing. Canakinumab treatment was associated with a decrease of IL-1β-induced downstream mediators including IL-1β itself, IL-1β pathway related genes, acute phase proteins such as serum amyloid (SAA) and C-reactive protein (CRP). This adds to the evidence that canakinumab neutralizes the activity and down-regulates the production of IL-1β in vivo.

Overall, the immunogenicity profile of canakinumab is entirely consistent across all disease areas. The incidence of treatment-emergent anti-drug antibodies (ADAs) remains very low, in the range of 0.5% to 2.9% and no clinical consequences to these detected antibodies are evident. No neutralizing antibodies were detected post-baseline in any study.

For further details, please refer to the [canakinumab Investigator's Brochure].

2 Rationale

2.1 Study rationale and purpose

As described in Section 1.2, inflammation (as measured through hs-CRP levels for example) plays an important role in the development of lung cancer. Prior publications examining hs-CRP levels in Stage I through Stage III NSCLC subjects show that higher stage is correlated with higher hs-CRP levels and poorer prognosis (Alifano et al 2011, Hara et al 2010, Vaguliene et al 2011). The cytokine interleukin-1β (IL-1β) is thought to be one of the mediators of pulmonary inflammation that promotes lung cancer and is critical in multiple steps of the carcinogenesis process. Canakinumab is a high-affinity human anti-interleukin-1β (IL-1β) monoclonal antibody approved for the treatment of subjects with various IL-1β driven auto-inflammatory diseases. Results from the CANTOS study indicated that canakinumab was associated with dose-dependent reductions in the risks of lung cancer occurrence and lung cancer mortality among study participants (Ridker 2017b). The maximal reduction in lung cancer occurrence and mortality was seen in subjects who received 300 mg s.c. every 3 months (highest dose group).

CANTOS (Study CACZ885M2301) is a double-blind, placebo-controlled, Phase-III trial of 10,061 randomized subjects who were in stable condition after a prior myocardial infarction (MI). It was designed to evaluate the efficacy, safety, and tolerability of canakinumab in

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combination with standard of care in the prevention of recurrent cardiovascular (CV) events in subjects with inflammatory atherosclerosis, as defined by the presence of hs-CRP, a known marker of inflammation, at levels of ≥2 mg/L. Subjects were ineligible if they had a pre-existing malignancy (other than basal cell skin carcinoma). Trial participants were randomized to receive treatment with one of three doses of canakinumab (300 mg, 150 mg, or 50 mg) or placebo administered subcutaneously every 3 months. Treatment was to be administered for a period of 6 years but was to be discontinued if any malignancy developed. The median age of subjects enrolled in CANTOS was 61.1 years, 25.7% of the subjects were female, and the 23.5% of subjects were current smokers with an additional 47.3% of subjects were former smokers. All subjects had a hs-CRP greater than 2 mg/L at entry and the median hs-CRP at entry was 4.2 mg/L for all subjects enrolled. The median hs-CRP at entry in CANTOS subjects who were subsequently diagnosed with cancer was 6.0 mg/L.

Data on cancer occurrence, as reported by the investigator, were collected as adverse events (AEs) and serious adverse events (SAEs). These events were adjudicated by an 8-member panel of external oncologists (the Malignancy Adjudication Committee (MAC)) blinded to treatment allocation. All malignancies that coded to a Medical Dictionary for Regulatory Activities (MedDRA (version 20.0)) preferred term (PT) of 'malignant or unspecified tumors' were forwarded to the MAC for assessment; the remit of the MAC was to categorize and evaluate whether investigator-reported malignancy AEs and SAEs occurred (or not). Any fatalities occurring during the trial were reviewed and categorized by the Clinical Endpoint Committee (CEC) for cause(s) of death. Deaths were adjudicated to be one of three major subtypes: (1) CV; (2) non-CV; and (3) unknown (presumed CV). Use of both the MAC and CEC was predefined in the study protocol.

Canakinumab treatment resulted in dose-dependent decreases in hs-CRP of 26-41% and IL-6 decreases of 25-43% (Ridker 2017b). As shown in Table 2-1, lung cancer incidence was less frequent in the 150 and 300 mg treated groups, with HR of 0.61 (95%CI 0.39-0.97) and 0.33 (95%CI 0.18-0.59), respectively (Ridker 2017b). Lung cancer mortality was significantly less in the canakinumab 300 mg treated group (HR=0.23 [95%CI 0.10-0.54)] and in the pooled canakinumab subjects (Ridker 2017b). Total cancer mortality was significantly lower in the pooled canakinumab groups versus the placebo group (p=0.0007), but only the 300 mg canakinumab group had statistically significant lowering (HR=0.49, 95%CI 0.31, 0.75, p=0.0009) (Ridker 2017b).

Table 2-1 Incidence rate per 100 subject years and hazard ratios for any cancer, fatal cancer, lung cancer and fatal lung cancer (Ridker 2017b)

Event	Placebo n=3344	Can* 50 mg s.c. quarterly n=2170	Can 150 mg s.c. quarterly n=2284	Can 300 mg s.c. quarterly n=2263	All Doses Can n=6717	p value (trend across doses)
Any Cancer						
Incidence rate(n)	1.88 (231)	1.85 (144)	1.69 (143)	1.72 (144)	1.75 (431)	0.31
HR (95% CI)	1 (ref)	0.99 (0.80-1.22)	0.90 (0.73-1.11)	0.91 (0.74-1.12)	0.93 (0.79-1.09)	
P	Ref	0.91	0.31	0.38	0.38	
Any Cancer (fatal)						

Incidence rate (n)	0.64 (81)	0.55 (44)	0.50 (44)	0.31 (.27)	0.45 (115)	0.0007
HR (95% CI)	1 (ref)	0.86 (0.59-1.24)	0.0.54-1.13)	0.49 (0.31-0.75)	0.71 (0.53-0.94)	
	Ref	0.42	0.19	0.0009	0.0158	
Lung Cancer						
Incidence rate (n)	0.49 (61)	0.35 (28)	0.30 (26)	0.16 (14)	0.27 (68)	<0.0001
HR (95% CI)	1 (ref)	0.74 (0.47-1.17)	0.61 (0.39-0.97)	0.33 (0.18-0.59)	0.55 (0.39-0.78)	
P	Ref	0.20	0.0337	<0.0001	0.0007	
Lung Cancer (fatal)						
Incidence rate (n)	0.30 (38)	0.20 (16)	0.19 (17)	0.07 (6)	0.15 (39)	0.0002
HR (95% CI)	1 (ref)	0.67 (0.37-1.20)	0.64 (0.36-1.14)	0.23 (0.10-0.54)	0.51 (0.33-0.80)	
P	Ref	0.18	0.13	0.0002	0.0026	
*Canakinumab						

Lung cancer occurrence and mortality

Canakinumab therapy was associated with a reduction in the risk of primary lung cancer occurrence relative to placebo, with a dose-dependent response evident across the canakinumab arms (Table 2-1). Maximal risk reduction was observed for the canakinumab 300 mg arm.

These data suggest that anti-inflammatory therapy with canakinumab targeting the IL-1β innate immunity pathway is associated with a dose-dependent reduction in the risk of primary lung cancer occurrence. Furthermore, treatment with canakinumab was also associated with a dose response in the risk reduction of primary lung cancer mortality.

Given the hypothesis-generating clinical data in CANTOS and the preclinical data that supports IL-1β plays a role in cancer development from initiation, promotion, angiogenesis, and through to metastasis (Dalgleish 2006, Mantovani 2008, O'Byrne 2000, O'Byrne 2001), a phase III study is proposed using canakinumab as adjuvant treatment in NSCLC subjects who are at high risk for recurrence.

2.2 Rationale for the study design

This is a multicenter, randomized, double blind, placebo-controlled study evaluating the efficacy and safety of canakinumab versus placebo as adjuvant therapy in adult subjects with stages AJCC/UICC v. 8 II-IIIA and the subset of IIIB with T>5cm N2 disease completely resected (R0) non-small cell lung cancer (NSCLC). The randomized, double-blind, placebo-controlled, multicenter, parallel-group design of this study minimizes allocation bias, balancing both known and unknown prognostic factors in the assignment of treatments. This phase III study CACZ885T2301 will enroll adult subjects with completely resected (R0) NSCLC AJCC/UICC v. 8 stages II-IIIA and IIIB (T>5cm and N2) disease. Subjects will complete standard of care adjuvant treatments for their NSCLC, including cisplatin-based chemotherapy and mediastinal radiation therapy (if applicable), before being screened or randomized for this study.

[redacted]

Table 2-2 Subject eligibility based on AJCC/UICC v.8 Stage Provided that All Tumor is completely Resected and Based Upon Pathological Staging (Adapted from Goldstraw, 2016)

Table 2-2 is removed. Refer to Section 5.1 for details on the inclusion/exclusion criteria.

Randomization will be stratified by the three following factors:

- AJCC/UICC v. 8 stage: IIA versus IIB versus IIIA versus IIIB with T>5cm, N2 disease
- Histology: squamous versus non-squamous

Both staging and histology are key determinants of prognosis.

- Region: Western Europe and North America vs. eastern Asia vs. Rest of the world (RoW), to account for possible differences in standard of care

The primary endpoint is disease-free survival (DFS) determined by local investigator assessment to reflect a reduced risk of lung cancer recurrence, with overall survival (OS) as a key secondary endpoint. Tumor assessments and follow-up visits for assessment of recurrence will be performed as per the NCCN guidelines for NSCLC version 8, 14 July 2017. It is postulated that 18 cycles (approximately one year) of adjuvant treatment will provide an acceptable benefit to risk ratio in subjects who have intermediate or high risk of developing disease recurrence.

Applicable for the sub-study*: Rationale to include the biomarker sub-study is to understand how resection surgery may impact the levels of hsCRP, other cytokines and biomarkers in blood. Adult subjects with NSCLC Stage IIA-IIIA, IIIB (T>5cm, N2 disease only) who are candidates for complete resection surgery (and therefore prospective candidates for the main study, CACZ885T2301) will be enrolled in the sub-study.

*For China only: biomarker collection is conditional upon approval from HA, EC and additional authorities (i.e. HGRAC).

2.3 Rationale for dose and regimen selection

The 200 mg s.c. every 3 weeks (q3w) dosing regimen of canakinumab is selected as the dosing schedule for the development program in NSCLC.

The every three week dosing regimen is feasible for canakinumab, based on its > 3 weeks half-life, and has proven its ability to neutralize IL-1β and suppress hs-CRP for at least 1 month across a wide range of doses. More importantly, given the evidence of the efficacy profile from the CANTOS study in which canakinumab shows no plateau effect in lung cancer risk reduction at 300 mg s.c. quarterly (q12w), and the comprehensive and well-established safety profile of canakinumab across a wide range of doses and dosing intervals studied in interventional trials, a 200 mg s.c q3w dosing schedule for canakinumab, which has an approximately equivalent total dose amount and similar predicted PK range as 300 mg s.c. q4w (a regimen already used in certain approved indications), is selected for the NSCLC development program to ensure a positive benefit/risk ratio. Every three weeks is preferred over every four weeks as the dosing regimens of combination partners (checkpoint inhibitors, chemotherapy) for future planned NSCLC trials often follow the every three week schedule.

[redacted]

Sub-sections below provide further details for the various considerations for dose and regimen selection:

PK and PD consideration:

Canakinumab displays PK properties typical of an IgG1 antibody, with a mean terminal half-life of 26 days. Every 3 weeks dosing schedule of canakinumab is feasible based on its half-life of 26 days, and its ability to suppress hs-CRP for at least 1 month as previously demonstrated in two single-dose phase 2 studies with dose ranges of 0.03 to 10 mg/kg i.v. and 25 to 300 mg s.c. ([Study CACZ885A2213] in diabetes and [Study CACZ885H2251] in gouty arthritis).

Efficacy consideration:

Canakinumab has demonstrated clinical benefit and is approved in 68 countries, including EU and US for the treatment of subjects with various IL-1β-driven auto-inflammatory diseases. For CAPS, the approved dosing regimen in US is 150 mg s.c. every 8 weeks (q8w) in adults (up-titration up to 600 mg s.c. q8w is allowed in EU). In other approved indications such as SJIA, TRAPS, HIDS/ MKD, and FMF, a starting dose at 4 mg/kg (max. 300 mg) every 4 weeks (q4w) or up-titration to 4 mg/kg or 300 mg q4w is required to achieve adequate efficacy in adults and children. If a full treatment response is subsequently achieved, the intensified dosing regimen of 300 mg q4w should be maintained. The different dosing regimens across indications could be due to differences in drug sensitivity across diseases likely caused by different clinical conditions and inflammatory status.

For the CANTOS study, the dose selection was primarily based on Study CACZ885I2202, a key dose finding study in subjects with diabetes, who were treated with 5, 15, 50 and 150 mg s.c. monthly doses, with 4-month treatment period (see [canakinumab Investigator's Brochure]).

As observed in Study CACZ885I2202, the largest observed reduction in hs-CRP at 4-month was found at a dose of 50 mg s.c. monthly. However, PK/PD modeling has predicted maximal hs-CRP reduction at doses between 75 and 100 mg s.c. monthly. Therefore, 50 mg s.c. monthly (or 150 mg s.c. quarterly) was considered as an efficacious dose while 15 mg s.c. monthly (or 50 mg s.c. quarterly) as a sub-optimal dose, and 100 mg s.c. monthly (or 300 mg s.c. quarterly) as the dose predicted to achieve the maximal hs-CRP reduction (see [Study M2301, Section 3.3] and [canakinumab Investigator's Brochure], [CACZ885I2202 study]).

Consistent with the modeling prediction, among the three dosing regimens tested in the CANTOS study (50, 150, and 300 mg s.c. quarterly), maximal hs-CRP reduction at 48 months was observed in the 300 mg s.c. quarterly dose (median reduction from baseline is 26%, 37%, and 41% in the 50 mg, 150 mg, and 300 mg groups, respectively), as compared with placebo, among atherosclerosis subject with elevated baseline hs-CRP who did not have a prior diagnosis of cancer (Ridker 2017a). In regards to clinical effects, 150 mg s.c. quarterly met the primary endpoint with 15% relative hazard reduction for MACE; 50 mg s.c. quarterly did not show significant effect compared to placebo, while 300 mg s.c. quarterly did not provide additional benefit versus 150 mg s.c. quarterly, with nearly identical magnitude of hazard reduction.

The CANTOS study also evaluated whether IL-1β inhibition might alter cancer occurrence and mortality as there is a strong inflammatory component to certain cancers, especially lung cancer. The results show that canakinumab, as compared to placebo, was associated with dose-

[redacted]

dependent risk reductions in lung cancer and lung cancer mortality. Unlike the cardiovascular indication, there is a clear differentiation in clinical benefits across all three dosing regimens, with the greatest risk reduction in lung cancer mortality achieved with the highest dose, 300 mg s.c. quarterly. Hazard ratios (95% confidence interval, P-value) were 0.67 (0.37-1.20,P=0.18), 0.64 (0.36-1.14,P=0.13), and 0.23 (0.10-0.54,P=0.0002) for the 50 mg, 150 mg, and 300 mg s.c. quarterly dose groups, respectively as reported by (Ridker 2017b). The dose-dependent pattern of hs-CRP reduction among subjects with lung cancer is also aligned with the clinical results, with the 300 mg group demonstrating the largest magnitude of reduction, relative to the other two treatment groups and placebo, with no saturating effect at 300 mg s.c. quarterly (Figure 2-1).

Given the CANTOS findings mentioned above, it appears that the link between the canakinumab dose needed for hs-CRP suppression, and the ultimate clinical effect, could differ across diseases. The different median baseline hs-CRP levels among canakinumab-treated subjects in CANTOS who were subsequently diagnosed with cancer compared to those who did not (median 6.0 mg/L [IQR: 3.5-11.5 mg/L] versus 4.2 mg/L [IQR: 2.8-7.1 mg/L], P<0.0001) (Ridker 2017b) likely reflect the different inflammatory status and risk for cancer. Notably, for subjects with higher baseline hs-CRP, the proportion of subjects with hs-CRP normalized to post-treatment target level (2.3 mg/L) is less, compared to subjects with lower baseline hs-CRP (Figure 2-2). This finding suggests that raising the dose and/or shortening the dosing interval may lead to better control of inflammation in subjects with higher baseline hs-CRP and deliver greater efficacy in subjects with higher baseline hs-CRP. Prior publications examining hs-CRP levels in Stage I through Stage III NSCLC subjects have shown that higher stage is correlated with higher hs-CRP levels and poorer prognosis (Alifano 2011, Hara 2010, Vaguliene 2011); these observations further support the need for a dose optimization in subjects with lung cancer.

Figure 2-1 **Median change from baseline in hs-CRP by treatment arms in confirmed lung cancer subjects from the CANTOS study**

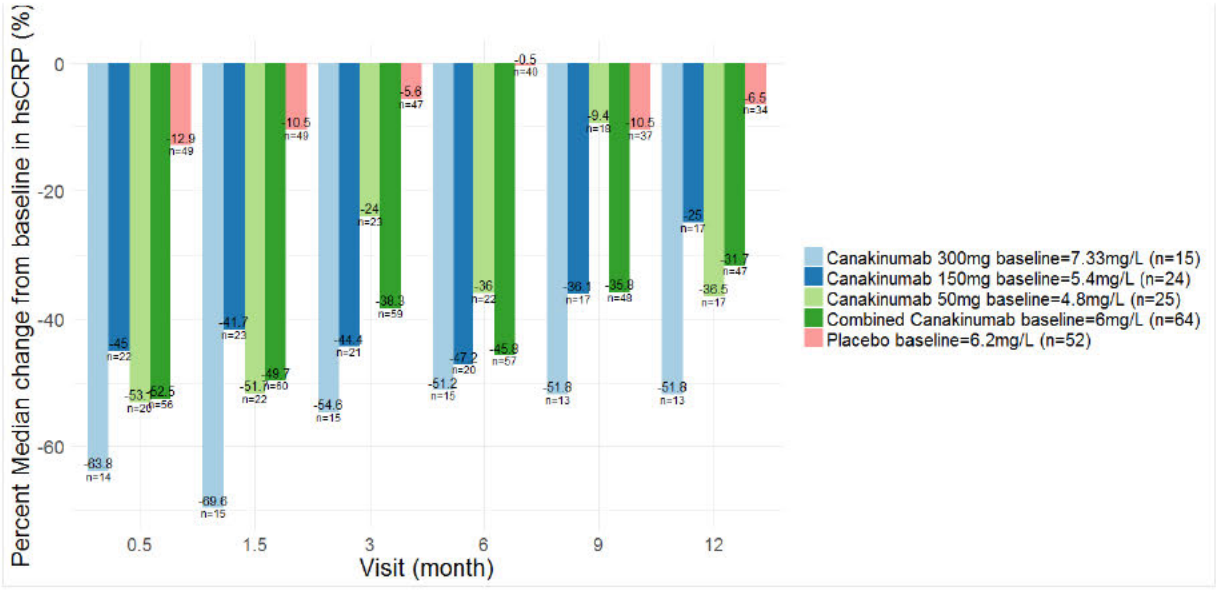
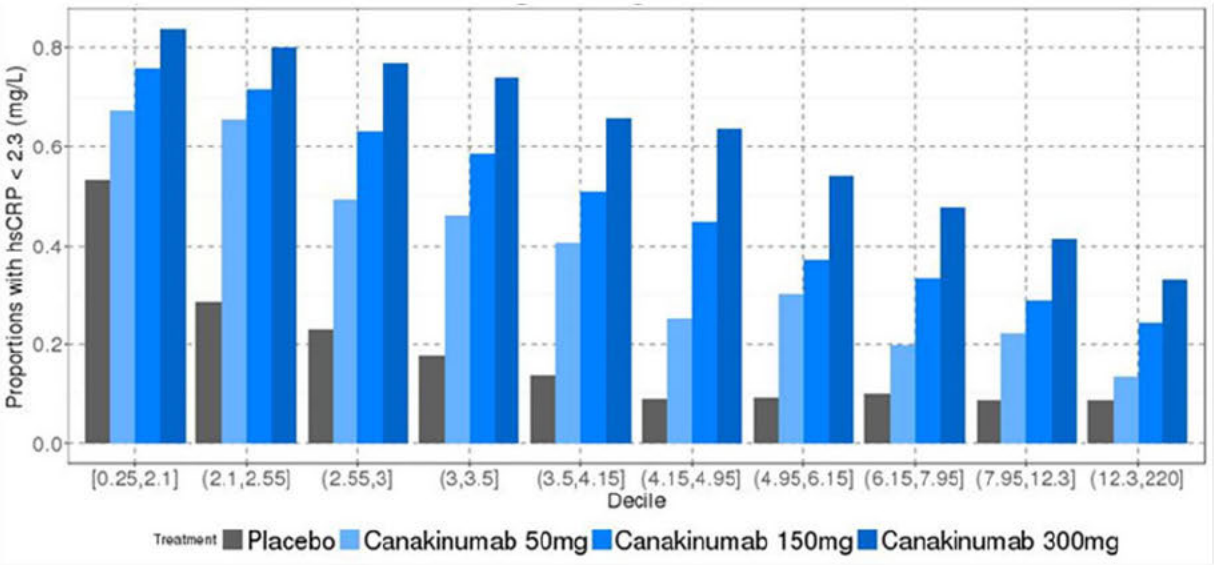


Figure 2-2 Proportions of subjects with hs-CRP < 2.3 mg/L by baseline hs-CRP deciles in all subjects from the CANTOS study



Median hs-CRP at 3 months was 2.3 mg/L based on all subjects in the Full Analysis Set.

Safety consideration:

Overall, canakinumab safety and tolerability findings across the three dosing regimens in CANTOS showed no new or unexpected signals and are similar to that reported in other populations, which shows it is well-tolerated across a wide range of dosing regimens (see [canakinumab Investigator's Brochure]). There were no meaningful differences between any of the canakinumab treatment groups and placebo in the overall incidence of AE or of SAEs in CANTOS (Section 2.6). Based on ~ 570 subjects treated with canakinumab in interventional trials in approved indications, the most frequently reported adverse drug reactions (ADRs) were infections, predominantly of the upper respiratory tract. Majority of the events were mild to moderate, although serious infections were observed. Early recognition of infection symptoms and immediate use of antibiotics with appropriate measures can prevent serious outcome of infections (Dinarello 2010). No neutralizing antibodies have been detected so far [Ilaris USPI, 2016] [Ilaris SmPC, 2017].

As described in the canakinumab IB across the completed and ongoing studies, higher canakinumab doses have been used before for other indications. In Study CACZ885G2301, the pivotal two-part phase 3 study of canakinumab with an open-label, single-arm active treatment (Part I, n=177) followed by a randomized, double-blind, placebo-controlled event-driven withdrawal design (Part II, n=50 on canakinumab arm) in SJIA subjects, canakinumab was given at a dose of 4 mg/kg (max. 300 mg) s.c. q4w with a median duration of exposure of 113 days in Part I and 222 days in Part II. In Study CACZ885G2301E1, the open-label extension study of canakinumab in SJIA subjects (n=270) enrolled from Study CACZ885G2301 and CACZ885G2305, canakinumab was given at a dose of 4 mg/kg (max. 300 mg) s.c. q4w for a total median duration of exposure of more than 2 years (166 weeks). In Study CACZ885A2201, a 12-week dose-finding study in methotrexate-resistant rheumatoid arthritis subjects, canakinumab was given at a dose of 300 mg s.c. q2w (n=64) or 600 mg i.v. loading dose plus 300 mg s.c. q2w (n=71) for a median duration of exposure of 85 days. About 80% of subjects

[redacted]

received study drug between 74 and 87 days. In Study CACZ885A2204, a 26-week phase II randomized, double-blind, placebo-controlled study in rheumatoid arthritis subjects, canakinumab was given at a dose of 600 mg i.v. q4w along with methotrexate. Of 52 subjects randomized to canakinumab plus methotrexate, 47 subjects received all 8 i.v. infusions of canakinumab, where the other 5 subjects received 2 to 7 i.v. infusions. This study reported no patient deaths and only 4 serious adverse events (SAEs); 2 in each treatment group. The SAEs in the methotrexate + placebo group were non-cardiac chest pain and upper gastrointestinal hemorrhage. The 2 SAEs in the methotrexate+ canakinumab group were elective cataract surgery, which was planned prior to study entry for pre-existing cataracts, and lip edema, which resulted in permanent discontinuation of canakinumab. The occurrence of infectious adverse events in the treatment groups was similar; 40.4% in the methotrexate + canakinumab group and 42.3% in the methotrexate + placebo group. No infectious SAEs were reported. These studies did not reveal clinically relevant differences in the types and severity of reported AEs across different dose groups. The AEs observed were mostly mild and moderate in severity, and similar to that of the placebo group. In addition, the AEs appear to be independent from duration of exposure and dose, and with consistent safety profile across indications.

In summary, with approval in many markets for use in multiple indications, the large body of accumulated safety data of canakinumab provides sufficient safety margin to evaluate canakinumab s.c. at the dose of 200 mg every three weeks.

2.4 Rationale for choice of combination drugs

Not Applicable

2.5 Rationale for choice of comparators drugs

Not applicable

2.6 Risks and benefits

Canakinumab is approved in several inflammatory disorders in many countries and is marketed under the trade name Ilaris. No dose limiting toxicities of canakinumab have been observed in subjects receiving doses of up to 600 mg I.V. q 4 weeks for 26 weeks (CACZ885A2204) or with chronic dosing of up to 300 mg s.c. every 4 weeks for over 2 years (CACZ885G2301, a two-part study).

The CANTOS study randomized 6717 subjects to canakinumab treatment. The most common adverse events (AEs), experienced by ≥ 10% of subjects, regardless of study drug relationship were viral upper respiratory tract infection and hypertension, in 12.5-13.9% and 10.1-10.3% of canakinumab-treated subjects versus 12.3% and 10.1% in the placebo group, respectively (Table 2-4). The most commonly reported serious adverse event (SAE) in ≥ 1% of subjects was pneumonia, which occurred in 3.4-3.7% in canakinumab-treated subjects versus 3.3% in the placebo group. Additional infectious SAEs included cellulitis and sepsis in 0.9-1.5% and 1.0-1.4% of canakinumab-treated subjects versus 3.3% and 0.8% in the placebo group, respectively. Deaths from infection and sepsis occurred in 0.07-0.19% and 0.15-2.1% in the canakinumab groups versus 0.06 and 0.13% in the placebo-treated subjects, respectively.

[redacted]

Safety in CANTOS

Table 2-3 Summary of AEs, SAEs, & discontinuations due to AEs & SAEs are comparable between canakinumab and placebo

Event	Can. 300 mg N=2263 n (%)	Can. 150 mg N=2285 n (%)	Can. 50 mg N=2170 n (%)	Placebo N=3348 n (%)
Subjects with at least one AE	1987 (87.8)	1970 (86.2)	1872 (86.3)	2914 (87.0)
Subjects with at least one SAE	836 (36.9)	812 (35.5)	741 (34.1)	1203 (35.9)
AEs suspected to be related to study drug	355 (15.7)	350 (15.3)	267 (12.3)	474 (14.2)
Subjects who permanently discontinued study drug due to AEs	175 (7.7)	164 (7.2)	142 (6.5)	244 (7.3)
Discontinued due to SAEs	135 (6.0)	130 (5.7)	117 (5.4)	197 (5.9)
Discontinued due to non-serious AEs	40 (1.8)	34 (1.5)	25 (1.2)	47 (1.4)
AEs leading to study drug interruption	268 (11.8)	270 (11.8)	228 (10.5)	399 (11.9)

Table 2-4 Summary of Adverse Events, regardless of relationship to study medication experienced by ≥ 10% of subjects in CANTOS

Preferred term	Can300mg N=2263 n (%)	Can150mg N=2285 n (%)	Can50mg N=2170 n (%)	Placebo N=3348 n (%)
Subjects with at least one AE	1987 (87.8)	1970 (86.2)	1872 (86.3)	2914 (87.0)
Viral upper respiratory tract infection	282 (12.5)	318 (13.9)	278 (12.8)	411 (12.3)
Hypertension	229 (10.1)	235 (10.3)	222 (10.2)	339 (10.1)
Angina pectoris	191 (8.4)	207 (9.1)	169 (7.8)	306 (9.1)
Back pain	189 (8.4)	202 (8.8)	171 (7.9)	301 (9.0)
Non-cardiac chest pain	190 (8.4)	196 (8.6)	157 (7.2)	304 (9.1)
Arthralgia	183 (8.1)	201 (8.8)	155 (7.1)	273 (8.2)
Upper respiratory tract infection	166 (7.3)	168 (7.4)	148 (6.8)	273 (8.2)
Bronchitis	153 (6.8)	183 (8.0)	135 (6.2)	269 (8.0)
Cough	169 (7.5)	169 (7.4)	129 (5.9)	252 (7.5)
Diarrhea	148 (6.5)	168 (7.4)	160 (7.4)	233 (7.0)
Dyspnea	157 (6.9)	147 (6.4)	137 (6.3)	236 (7.0)
Urinary tract infection	159 (7.0)	164 (7.2)	121 (5.6)	224 (6.7)
Influenza	162 (7.2)	162 (7.1)	126 (5.8)	205 (6.1)
Pain in extremity	160 (7.1)	155 (6.8)	110 (5.1)	227 (6.8)
Edema peripheral	146 (6.5)	153 (6.7)	142 (6.5)	197 (5.9)
Dizziness	128 (5.7)	138 (6.0)	145 (6.7)	212 (6.3)
Pneumonia	132 (5.8)	153 (6.7)	128 (5.9)	208 (6.2)
Headache	145 (6.4)	120 (5.3)	126 (5.8)	196 (5.9)
Fatigue	125 (5.5)	108 (4.7)	93 (4.3)	183 (5.5)
Osteoarthritis	109 (4.8)	95 (4.2)	94 (4.3)	202 (6.0)

[redacted]

The most common AE in CANTOS was upper respiratory infection and the most common SAE was pneumonia.

The occurrence of sepsis was reported in a slightly higher percentage of subjects 1.0-1.4 % in the canakinumab-treated groups versus 0.8% in the placebo group.

Due to the mode of action of all inhibitors of the IL-1 pathway, infection is an important concern. Subjects should be closely monitored for signs or symptoms of infection and appropriate treatment instituted in a timely manner (see Section 6.3.3). Reported infections are usually mild to moderate in severity. Although the majority of reported infections resolved spontaneously or with standard therapy, severe, serious and fatal infections have been reported. Relevant to increased infections, mild to moderate neutropenia has been reported. No CTC grade 3 or 4 episodes of neutropenia or thrombocytopenia have been reported in clinical trials with canakinumab. Inclusion/exclusion criteria (Section 5), on treatment visits and monitoring (Section 7) as well as dose adjustments (Section 6) have been included in the study protocol to mitigate these risks.

Canakinumab showed a dose-related reduction in the occurrence of lung cancer in the CANTOS study, as detailed in Section 2.1 and Section 2.3. Given an expected benefit of a 28.4% decrease in the recurrence of NSCLC and a manageable risk of potential infections, canakinumab has a favorable risk-benefit ratio in the defined enrollment population.

2.7 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster,), mitigation procedures may be required to ensure subject safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis/Sponsor prior to implementation of mitigation procedures and permitted/approved by local or regional health authorities and ethics committees as appropriate.

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 and Table 3-2 below.

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4.
The primary objective is to compare the Disease-free survival (DFS) in the canakinumab versus placebo arms as determined by local investigator assessment.	DFS determined by local investigator assessment	
Key secondary		Refer to Section 10.5.1.
To compare overall survival (OS) in the canakinumab arm versus placebo arm	OS	
Other secondary		Refer to Section 10.5.2, Section 10.5.3, Section 10.5.4, Section 10.5.6,
1. To compare DFS by local investigator assessment and OS in the canakinumab versus placebo arms in subgroups defined respectively by PD-L1 and CD8 expression levels	1. DFS by local investigator assessment and OS in PD-L1 and CD8 subgroups	
2. To compare lung cancer specific survival in the canakinumab arm versus placebo arm	2. Lung cancer specific survival (LCSS)	
3. To characterize the safety profile of canakinumab	3. Frequency of AEs, ECGs and laboratory abnormalities	
4. To characterize the pharmacokinetics of canakinumab therapy	4. Serum concentration-time profiles of canakinumab and appropriate individual PK parameters based on population PK model	
5. To characterize the prevalence and incidence of immunogenicity (anti-drug antibodies, ADA) of canakinumab	5. Anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment of canakinumab	
6. To assess the effect of canakinumab versus placebo on PROs (EORTC QLQ-C30 with QLQ-LC13 incorporated and EQ-5D) including functioning and health-related quality of life	6. Time to definitive 10 point deterioration symptom scores of pain, cough and dyspnea per QLQ-LC13 questionnaire are primary PRO variables of interest. Time to 10 point definitive deterioration of global health status/QoL, shortness of breath and pain per QLQ-C30 questionnaire, time to first deterioration for symptom scores of pain, cough, dyspnea per QLQ-LC13 questionnaire, time to first 10 point deterioration for global health status/QoL, shortness of breath and pain per QLQ-C30 questionnaire together with the utilities derived from EQ-5D-5L are secondary PRO variables of interest	

[redacted]

Objective	Endpoint	Analysis
[redacted]		

Table 3-2 Objectives and related endpoints applicable for sub-study (CACZ885T2301A)*

Objective	Endpoint	Analysis
For all subjects participating into sub-study: • To assess the levels of hs-CRP, other cytokines and additional biomarker levels in blood at pre- and post-surgery.	• Summary statistics of hs-CRP and other PD biomarkers	Refer to Section 10.6.1
For subjects who will also enroll into the main study: • To determine whether there is an association between pre- and post-surgery biomarker levels with canakinumab efficacy (e.g. DFS, OS).	• DFS and OS by hs-CRP and other PD biomarkers	Refer to Section 10.6.1

*For China only: biomarker collection is conditional upon approval from HA, EC and additional authorities (i.e. HGRAC).

[redacted]

4 Study design

4.1 Description of study design

This phase III study CACZ885T2301 (main study) will enroll adult subjects with completely resected (R0) NSCLC AJCC/UICC v. 8 stages II-IIIA and IIIB (T>5cm N2) disease.Subjects may be screened after undergoing complete surgical resection of their NSCLC and having R0 status confirmed (negative margins on pathologic review), after completing adjuvant cisplatin-based doublet chemotherapy if applicable, (radiation therapy is allowed if indicated as per local guidelines or practice) and after all entry criteria are met. Subjects must not have had preoperative neo-adjuvant chemotherapy or radiotherapy to achieve the R0 status.

NSCLC subjects who are candidates for complete resection surgery (and therefore prospective candidates for the main study, CACZ885T2301) will be asked to participate in a biomarker sub-study (CACZ885T2301A). **Unless otherwise noted that it is specific for the sub-study, the protocol will be referring to the conduct of the main study.**

In this sub-study, an additional consent will be obtained to collect pre- and post-surgery blood samples to understand how resection surgery may impact hs-CRP, other cytokines and additional biomarker levels in blood (Figure 4-2).

These subjects may later be eligible for the main study after the completion of the post-surgery standard of care treatment (i.e. cisplatin based chemotherapy with or without radiation). Further details are provided in Section 7.2.4.2.

In the main study, approximately 1500 subjects will be randomized 1:1 to canakinumab, 200 mg subcutaneously (s.c.) every 3 weeks or matching placebo, s.c., every 3 weeks (Figure 4-1). Randomization will be stratified by AJCC/UICC v. 8 stage: IIA versus IIB versus IIIA versus IIIB with T>5cm, N2 disease; Histology: squamous versus non-squamous; and Region: Western Europe and North America vs. eastern Asia vs. Rest of the world (RoW). Subjects will continue their assigned treatment until they complete 18 cycles or experience any one of the following: NSCLC disease recurrence as determined by Investigator, unacceptable toxicity that precludes further treatment, treatment discontinuation at the discretion of the Investigator or subject, or start of a new antineoplastic therapy, or death, or lost to follow-up, whichever occurs first. It is postulated that the one year duration of adjuvant treatment will provide an acceptable benefit in subjects who have intermediate or high risk of developing disease recurrence. If NSCLC disease recurrence is not observed during the treatment phase, subjects will be followed until NSCLC disease recurrence, withdrawal of consent by the subject, subject is lost to follow up, death or the sponsor terminates the study for up to five years. All subjects who discontinue from the study treatment will be followed up every 12 weeks for survival until the final overall survival (OS) analysis or death, lost to follow-up or withdrawal of consent for survival follow-up.

The purpose of this prospective, multicenter, randomized, double blind, placebo-controlled phase III study is to evaluate the efficacy and safety of canakinumab as adjuvant therapy, following standard of care for completely resected (R0) AJCC/UICC v. 8 stages II-IIIA and stage IIIB (T>5cm N2) NSCLC subjects.

[redacted]

Standard of care includes complete resection of the NSCLC with margins free of cancer. At a minimum, two cycles of cisplatin-based doublet chemotherapy are required for all stage IIB-IIIA and IIIB (T>5cm N2) disease subjects; chemotherapy is recommended but not mandatory for stage IIA with no nodal involvement. Radiation therapy is allowed if indicated as per local guidelines or practice. All subjects must have had complete surgical resection of their NSCLC to be eligible for study entry; and margins must be pathologically reviewed and documented as negative. Comparisons will be made between the arms for efficacy: DFS, OS, LCSS and Quality of Life measures (EQ-5D-5L and EORTC QLQ-C30/LC13) and for safety.

Figure 4-1 Study Design

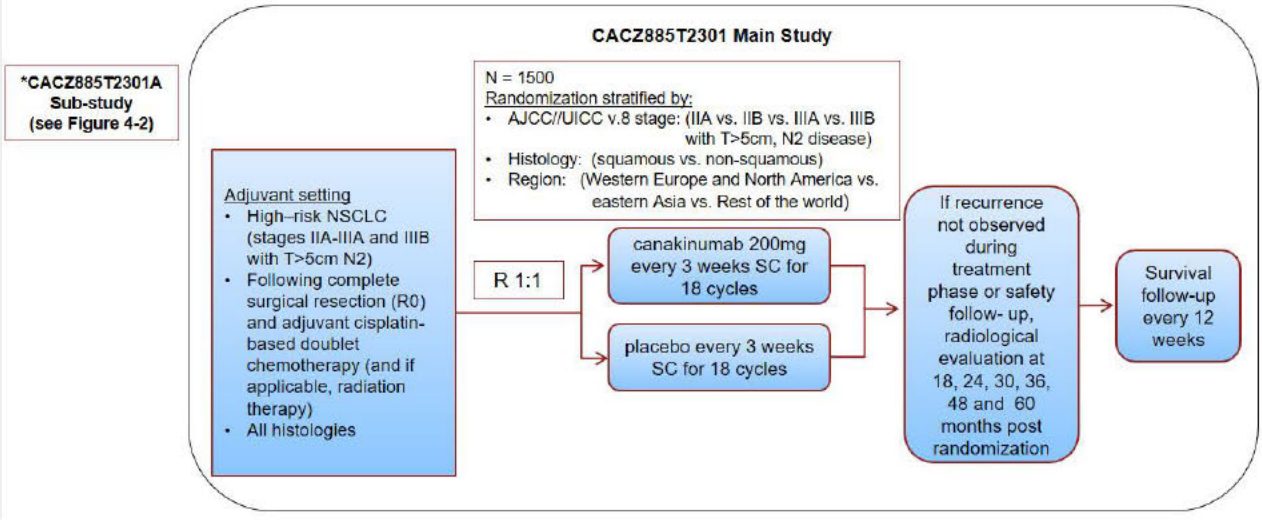
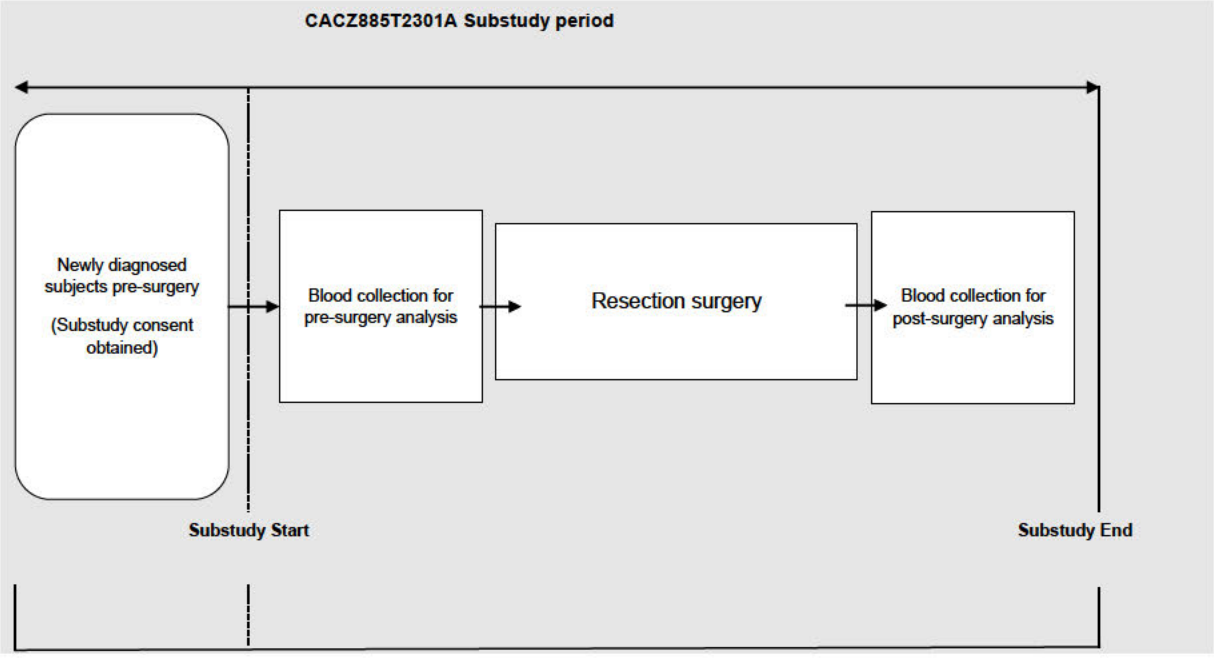


Figure 4-2 Biomarker sub-study design



4.2 Timing of interim analyses and design adaptations

One interim analysis (IA) will be performed for DFS for futility when approximately 196 (50%) of the 392 DFS events have been observed. The primary intent of this IA is to determine whether there is a need to stop the study early for lack of efficacy (futility, there is no plan to stop the study for efficacy at this IA).

In addition, a hierarchical testing procedure will be adopted and the statistical tests for OS will be performed only if the primary efficacy endpoint DFS is statistically significant.

A maximum of three analyses are planned for OS (OS will be statistically tested only if DFS meets statistical significance at final DFS analysis):

- At the time of final DFS analysis (provided DFS is statistically significant at final DFS analysis), at which point a total of approximately 318 (63%) deaths are expected
- An additional IA for OS when a total of approximately 418 (83%) deaths are expected (expected 52 months from the date of the first subject being randomized)
- A final analysis for OS when approximately 504 deaths are expected (expected 63 months from the date of the first subject being randomized).

4.3 Definition of end of study

The primary analysis of DFS will occur when approximately 392 DFS events are reached, (refer to Section 10.4). At this time, the primary clinical study report (CSR) will be produced.

After the primary analysis of DFS, the study will remain open provided the DFS demonstrates treatment benefit. Subjects still being followed on the study after the primary analysis time point will continue as per the schedule of assessments.

The study will end once the final OS analysis is performed when approximately 504 deaths are observed or when statistical significance is reached for OS analysis at interim analysis (refer to Section 10.7) and the final analysis of study data is conducted. All available data from all subjects up to this cutoff date will be analyzed.

If the primary analysis of DFS does not demonstrate treatment benefit, the follow-up for OS will end.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the subject should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a discontinued or withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

[redacted]

5 Population

5.1 Subject population

This phase III study CACZ885T2301 will enroll adult subjects with completely resected (R0) NSCLC AJCC/UICC v. 8 stages II-IIIA and IIIB (T>5 cm N2) disease. These groups have been included to allow all subjects that are able to achieve complete resection of their cancer with negative margins (R0 status). The inclusion of these subjects is consistent with other adjuvant NSCLC studies as they are at a significant risk of relapse to merit inclusion in adjuvant trials.

See inclusion criteria (Section 5.2) for complete information on required adjuvant cisplatin-based doublet therapy. Subjects will be randomized after completing adjuvant cisplatin-doublet chemotherapy and meeting entry criteria.

The investigator or designee must ensure that only subjects who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

Applicable for the sub-study: The sub-study, CACZ885T2301A, will enroll adult subjects with NSCLC Stage IIA-IIIA, IIIB (T>5cm, N2 disease only) who are candidates for complete resection surgery (and therefore prospective candidates for the main study, CACZ885T2301). Biomarker samples pre- and post-surgery will be collected from these subjects. See Sections 5.2.1 and Section 7.2.4.2 for further details.

5.2 Inclusion criteria (applicable for main study)

Subjects eligible for inclusion in this study have to meet **all** of the following criteria at the time of screening:

1. Written informed consent must be obtained prior to any screening procedures.
2. Age ≥ 18 years

3a. Completely resected (R0) NSCLC AJCC/UICC v. 8 stage IIA-IIIA and IIIB (T>5cm, N2 disease only). Minimal treatments considered adequate prior to study enrollment are:

Treatment modality	• Minimum extent of treatment required prior to study entry
Surgery	• Complete surgical resection (R0) is mandatory for all subjects. • R0 is considered when in microscopic pathology evaluation there are no cancer cells in the surgical margin or within 1mm of the margin.
Chemotherapy	• Cisplatin-based chemotherapy is mandatory for all subjects (Exception: In subjects with stage IIA disease with no nodal involvement, cisplatin-based chemotherapy can be administered if recommended by the treating physician). • When required, a minimum of two cycles of cisplatin-based chemotherapy is mandatory, after which additional therapies can be given based upon local clinical practice and/or guidelines. • Typically, chemotherapy is initiated within 60 days of surgery.
Radiation therapy	• Radiation therapy is allowed if indicated as per local guidelines or practice.

The maximum number of days allowed from surgery to randomization is:

- **70 days** if subjects were treated with surgery, but did not receive chemotherapy or radiation.
- **182 days** if subjects were treated with surgery and chemotherapy, but no radiation.
- **259 days** if subjects were treated with surgery, chemotherapy and radiation.

[redacted]

Note:

- Subjects may enter the study earlier than maximum number of days allowed, if fully recovered from surgery and adjuvant therapies.
- A window of +7 days is allowed to accommodate subject scheduling if needed.
- In case of case of chemotherapy treatment delays due to toxicities, additional window of +14 days is allowed.

4. Criterion removed.
5. Criterion removed.
6. Criterion removed.

7a. Subjects must have recovered from all toxicities related to prior systemic therapy to grade ≤ 1 (CTCAE v 5.0). Exception to this criterion: subjects with any grade of alopecia, neuropathy (grade ≤2), and subjects meeting the laboratory specifications described in inclusion 8.

8. Subjects must have adequate organ function including the following laboratory values at the screening visit:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Platelets ≥ 100 x 10^9/L
- Hemoglobin (Hgb) > 9 g/dL
- Creatinine clearance greater than 45 mL/min using Cockcroft-Gault formula
- Total bilirubin ≤ 1.5 x ULN
- Aspartate transaminase (AST) ≤ 3 x ULN
- Alanine transaminase (ALT) ≤ 3 x ULN

9. ECOG performance status (PS) of 0 or 1.
10. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.

5.2.1 Inclusion criteria applicable for sub-study (CACZ885T2301A)

1. Written informed consent to sub-study must be obtained prior to any collections.
2. Age ≥ 18 years
3. Subjects with NSCLC Stage IIA-IIIA, IIIB (T>5cm, N2 disease only) who are candidates for complete resection surgery.

5.3 Exclusion criteria (applicable for main study)

Subjects eligible for this study must not meet **any** of the following criteria at the time of screening:

1. Subjects with unresectable or metastatic disease, positive microscopic margins on the pathology report, and/or gross disease remaining at the time of surgery.
2. Subjects who received any neoadjuvant treatment.

3a. Presence or history of a malignant disease, other than the resected NSCLC, that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers,

[redacted]

completely resected carcinoma in situ of any type and hormonal maintenance for breast and prostate cancer >3 years.

4a. History of clinically significant interstitial lung disease (≥ grade 2). If radiological changes alone are present at baseline (CTC grade 1 interstitial lung disease) should be added to past medical history/concurrent medical conditions at baseline.

5a. History or current diagnosis of cardiac disease, including any of the following:

- recent myocardial infarction or coronary artery bypass graft (CABG) surgery within last 6 months,
- uncontrolled CHF,
- unstable angina (within last 6 months),
- clinically significant (symptomatic) cardiac arrhythmias

6a. Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting cycle 1 day 1 or subjects who have not recovered from radiotherapy-related toxicities.

7. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior to randomization or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and subjects can be enrolled in the study ≥1 week after the procedure.

8. Uncontrolled diabetes as defined by the investigator.

9. Known active or recurrent hepatic disorder including cirrhosis, hepatitis B and C (positive or indeterminate central laboratory results).

10a. Subjects must be evaluated for tuberculosis as per local treatment guidelines or clinical practice. Subjects with active tuberculosis are not eligible. In subjects without active tuberculosis, if the results of the evaluation require treatment per local guidelines, then the treatment should be initiated before randomization (unless otherwise required by Health Authorities or IRB in which case curative treatment must be completed prior to screening).

11a. Subjects with suspected or proven immunocompromised state or infections, including:

a. Known history of testing positive for Human Immunodeficiency Virus (HIV) infections.
b. Those with any other medical condition such as active infection, treated or untreated, which in the opinion of the investigator places the subject at an unacceptable risk for participation in immunomodulatory therapy. Note: Subjects with localized condition unlikely to lead to a systemic infection (e.g. chronic nail fungal infection) are eligible.
c. Allogeneic bone marrow or solid organ transplant
d. Those requiring systemic or local treatment with any immune modulating agent in doses with systemic effects e.g.:
    i. Prednisone >20 mg (or equivalent) oral or intravenous daily for >14 days;
    ii. Prednisone > 5 mg and ≤ 20 mg (or equivalent) daily for > 30 days;
    iii. Equivalent dose of methotrexate >15 mg weekly.
    iv. Note: Daily glucocorticoid-replacement for conditions such as adrenal or pituitary insufficiency is allowed. Topical, inhaled or local steroid use in doses that are not

[redacted]

considered to cause systemic effects are permitted. Steroids for pre-medication related to chemotherapy as per local standard of care are permitted.

12a. Live or attenuated vaccination within 3 months prior to first dose of study drug (e.g. MMR, Yellow Fever, Rotavirus, Smallpox, etc.).

13. Prior treatment with canakinumab or drugs of a similar mechanism of action (IL-1β inhibitor).

14. History of hypersensitivity to canakinumab or drugs of a similar class.

15. Subjects who have received an investigational drug or device within 30 days prior to first dose of study drug or those who are expected to participate in any other investigational drug or device during the conduct of the study.

16. Subjects who received any biologic drugs targeting the immune system at any time.

17. Any medical condition resulting in a life expectancy of less than 5 years, other than the risk for recurrent lung cancer.

18. Pregnant or nursing 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

19a. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and for up to 3 months after last dose of study drug. Effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/ vaginal suppository
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. Prior to entry into this study, cisplatin-based chemotherapy, which may be toxic to the fetus, may be given. The time between the end of cisplatin-based chemotherapy and the start canakinumab/placebo treatment is variable, resulting in a variable need for continuation of highly effective contraception.

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks prior to first dose of study drug. In the case of oophorectomy alone, only when the reproductive status

[redacted]

of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

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

6 Treatment

6.1 Study treatment

Canakinumab (ACZ885) or matching placebo solution for injection will be provided by Novartis as ready-to-use pre-filled syringes to be administered by study center personnel.

Two strengths and respective corresponding matching placebos will be supplied:

- Canakinumab 50 mg in 0.5 mL solution for injection and one placebo formulation matching to this active drug formulation.
- Canakinumab 150 mg in 1 mL solution for injection and one placebo formulation matching to this active drug formulation.

6.1.1 Dosing regimen

The study is double-blind. All eligible subjects will be randomized to one of the following two treatment arms in a 1:1 ratio:

- Canakinumab 200 mg s.c. on day 1 of every 21-day cycle for 18 cycles
- Placebo s.c. on day 1 of every 21-day cycle for 18 cycles

The study drug will be given as subcutaneous injections on C1D1 and then every cycle (21 days) for 18 cycles. All injections (one syringe of 1 ml and one syringe of 0.5 ml) will be administered at study sites by trained site staff, facilitating both compliance and long-term follow-up for both safety and efficacy outcomes.

Study drug should not be administered on the same day or same limb as non-live vaccines in order to distinguish any potential injection related reactions.

Table 6-1 Injection Description

Treatment Groups	Injections at all planned dosing visits
Canakinumab 200 mg sc	1 x canakinumab 150 mg and 1 x canakinumab 50 mg
Placebo	1 x placebo matching canakinumab 150 mg and 1 x placebo matching canakinumab 50 mg

6.1.2 Ancillary treatments

Not applicable

[redacted]

6.1.3 Rescue medication

Not applicable

6.1.4 Guidelines for continuation of treatment

Not applicable

6.1.5 Treatment duration

Subjects will be treated with canakinumab or placebo for 18 cycles (approximately 54 weeks) or until they experience any of the following: first NSCLC recurrence as determined by the investigator, unacceptable toxicity that precludes further treatment, treatment discontinuation at the discretion of the Investigator or subject, or start of a new antineoplastic therapy, or death, or lost to follow-up, whichever occurs first.

6.2 Dose escalation guidelines

Not applicable

6.2.1 Starting dose rationale

The 200 mg s.c. every 3 weeks (q3w) dosing regimen of canakinumab is selected as the dosing schedule for the development program in NSCLC. This dosing regimen is selected based on the pharmacokinetic (PK) and pharmacodynamics (PD) properties of canakinumab, the observed safety, biomarker and efficacy data from the CANTOS study, the safety data from completed and ongoing canakinumab studies, as well as the dosing schedule for combination drugs for future NSCLC studies (See Section 2.3).

6.2.2 Provisional dose levels

Not applicable

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For subjects who do not tolerate the protocol-specified dosing schedule, dose interruptions are either recommended or mandated in order to allow subjects to continue the study treatment. **There are no dose reductions allowed in this study.**

These dose modifications are summarized in Table 6-2. If mandatory dose interruptions are not performed, deviations will be noted. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2 or listed in Section 7.1.4.

Scheduled dosing of study drug may, at the discretion of the Investigator, be delayed by up to 7 days if subjects present with conditions that require withholding of study drug, e.g., presence of skin ulcer or evidence for active infection (treated or untreated). Outside of this 7 day window, the dose will be considered missed. After a dose is missed, the subject should resume treatment on the original schedule of study drug administration per C1D1. If a subject requires a dose interruption of greater than 42 days from the intended day of the next scheduled dose,

[redacted]

then the subject must be discontinued from the study. Subjects who discontinue the study for a study related adverse event or an abnormal laboratory value must be followed as described in Section 7.1.4.

Infections

Infections are the most common adverse event and may be related to study medication. Subjects should be followed closely for any signs or symptoms of infection and receive prompt appropriate treatment for any suspected infection. Respiratory infections are common in subjects who have had lung cancer, in part due to underlying lung diseases such as chronic obstructive pulmonary disease and other smoking or second-hand smoke related lung diseases. Subjects will have a urinalysis performed at every study visit (screening and throughout the study treatment); occult urinary tract infections, if not promptly treated may result in urosepsis. Site personnel should be aware of this concern and review urinalysis results and take action if treatment of the subject for a urinary tract infection is required.

[redacted]

Table 6-2 Criteria for dose interruption and re-initiation of treatment for adverse drug reactions

Dose Schedule modifications for Canakinumab[a]	
Worst toxicity *CTCAE Version 5.0 during a cycle of therapy*	
Infections fall under many CTC terms	
Grade 1	Recommendation: maintain dose level
Grade 2	Recommendation: maintain dose level
Grade 3	Recommendation: Omit dose until resolved to ≤ Grade 2, then maintain dose level
Grade 4	Mandatory: Permanently discontinue study medication
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm3)	May maintain dose level
Grade 2 (ANC < 1500 - 1000/mm3)	May maintain dose level
Grade 3 (ANC < 1000 - 500/mm3)	Mandatory: Omit dose until resolved to ≤ Grade 2, then maintain dose level
Grade 4 (ANC < 500/mm3)	Mandatory: Permanently Discontinue study medication
Febrile neutropenia (ANC < 1.0 x 109/L, fever ≥ 38.5°C)	Mandatory: Permanently Discontinue study medication
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm3)	May maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm3)	May maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm3)	Recommendation: Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, permanently discontinue study medication (mandatory)
Grade 4 (PLT < 25,000/mm3)	Mandatory: permanently discontinue study medication

[redacted]

Dose Schedule modifications for Canakinumab[a]	
Worst toxicity *CTCAE Version 5.0 during a cycle of therapy*	
Investigations (Renal)	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	May maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN) *Grade 3 (> 3.0 - 6.0 x ULN)*	Recommendation: May maintain dose level Recommendation: Omit dose until resolved to ≤ Grade 2 or baseline. If not resolved within 14 days, then permanently discontinue subject from study drug treatment
Grade 4 (> 6.0 x ULN)	Mandatory: Discontinue subject from study drug treatment
Investigations (Hepatic)	
Isolated total Bilirubin elevation	
Any elevation > ULN: Grade 2 (*> 1.5 - 3.0 x ULN)* *Grade 3 (> 3.0 - 10.0 x ULN)** *Grade 4 (> 10.0 x ULN)**	• Fractionate bilirubin, evaluate for cholestatic liver injury (ALP) or alternative causes of bilirubin elevation (e.g. disease progression [imaging]). Treat alternative causes according to local institutional guidelines. • Maintain treatment. Repeat LFTs[b] within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline. • Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline. • See footnote** - otherwise discontinue study treatment.
**Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), continue treatment at the discretion of the investigator.*	
***An isolated bilirubin elevation is not typical for drug-induced liver injury. Bilirubin can be elevated either as part of a "Hy's law" constellation with a preceding elevation of ALT/AST, or as part of a cholestatic reaction with simultaneous elevation of other cholestatic parameters (ALP, GGT). Isolated bilirubin can be seen in conjunction with drugs that inhibit bilirubin conjugation or excretion, but both scenarios do not typically represent liver injury. Alternative causes of bilirubin elevation should therefore, be ruled out before basing dose modification decisions on bilirubin values alone.*	
Isolated AST or ALT elevation	
With normal baseline AST/ALT: *> ULN - 3.0 x ULN*	*Recommendation: Maintain dose level*

[redacted]

Dose Schedule modifications for Canakinumab[a]	
Worst toxicity *CTCAE Version 5.0 during a cycle of therapy*	
> 3.0 - 5.0 x ULN	Recommendation: Maintain dose level. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN Maintain dose level
• Grade 3: AST or ALT (>5.0 – 20.0) x ULN If AST or ALT > 5.0 - 10.0 x ULN If AST or ALT > 10.0 - 20.0 x ULN • *Grade 4: AST or ALT (> 20.0 x ULN)*	• Interrupt treatment. Repeat LFTsb within 48-72 hours, then monitor LFTsb weekly until recovery to Grade ≤1 or to baseline, then resume study drug. • If interruption > 42 days then subject must be discontinued. • Interrupt treatment. Repeat LFTsb within 48-72 hours, then monitor LFTsb weekly until recovery to Grade ≤1 or to baseline, then resume study drug. • If interruption > 42 days then subject must be discontinued. Permanently discontinue study treatment.
With abnormal baseline ALT/AST (up to Grade 1: ≤ 3.0 ULN):	
• ALT/AST > 2.0 x baseline AND > 5.0 x ULN • ALT/AST > 3.0 x baseline AND >10 x ULN • Grade 4: AST or ALT (>20 x ULN)	• Interrupt treatment. Repeat LFTsb within 48-72 hours, then monitor LFTsb weekly until recovery to baseline, then resume study drug. • If interruption > 42 days then subject must be discontinued. • Interrupt treatment. Repeat LFTsb within 48-72 hours, then monitor LFTsb weekly until recovery to baseline, then resume study drug. • If interruption > 42 days then subject must be discontinued. Permanently discontinue study treatment.
Concomitant elevations of AST or ALT and total bilirubin[c]	
With normal baseline LFTs: Grade 2 ALT/AST (>3.0 x ULN) with bilirubin > 2.0 x ULN without evidence of cholestasis[d] (unless Gilbert's syndrome)	Interrupt study treatment. Assess if case is true DILI (Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), continue treatment at the discretion of the investigator.) **If DILI confirmed** - Permanently discontinue **If Not DILI** – interrupt treatment. Treat the identified cause according to institutional guidelines. Repeat LFTs within 48-72 hours, then monitor weekly, till enzyme levels resolve to ≤Grade 1 or Baseline.

[redacted]

Dose Schedule modifications for Canakinumab[a]	
Worst toxicity *CTCAE Version 5.0 during a cycle of therapy*	
	Note: For additional information on follow-up of potential drug induced liver injury cases, refer to Section 6.3.3.2.
With abnormal baseline LFTs: ALT or AST >2 x baseline OR ALT or AST >8 x ULN *(whichever is lower)* *combined with total bilirubin >2.0x ULN*	After recovery, re-administration of study treatment could be considered only if Investigator assesses benefit to outweigh the risk. Note: For additional information on follow-up of potential drug induced liver injury cases, refer to Section 6.3.3.2.
Investigation (metabolic)	
Asymptomatic amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	May maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN; > 2.0 -5.0 X ULN and asymptomatic)	May maintain dose level
Grade 3 (> 2.0 - 5.0 x ULN with signs or symptoms; > 5.0 ULN and asymptomatic)*	Recommendation: Omit dose : If resolved to grade ≤ 1 or baseline in ≤ 7 days, then maintain dose level If resolved to grade ≤ 1 or baseline in > 7 days, then discontinue subject from study medication (mandatory)
Grade 4 (> 5.0 x ULN and with signs or symptoms)*	Mandatory: Discontinue subject from study drug treatment.
**Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 2 weeks of the first occurrence of any ≥ Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again after restarting therapy, subjects will be discontinued permanently from study treatment.*	
Vascular disorders	
Hypertension	
CTCAE Grade 3	Recommendation: Omit dose until resolved ≤ Grade 1, then maintain level
CTCAE Grade 4	Mandatory: Discontinue subject from study drug treatment
Gastrointestinal	
Pancreatitis	
Grade 2	Recommendation: Maintain dose level
Grade ≥ 3	Mandatory: Discontinue subject from study drug treatment

[redacted]

Dose Schedule modifications for Canakinumab[a]	
Worst toxicity *CTCAE Version 5.0 during a cycle of therapy*	
Diarrhea *Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea*	
Grade 1	May maintain dose level but initiate anti-diarrhea treatment
Grade 2	Recommendation: Omit dose until resolved to ≤ Grade 1, then maintain dose level.
Grade 3	Recommendation: Discontinue subject from study drug treatment
Grade 4	Mandatory: Discontinue subject from study drug treatment
Skin and subcutaneous tissue disorders	
Rash/photosensitivity	
Grade 1	May maintain dose level. Consider to initiate/institute appropriate skin toxicity therapy (such as antihistamines and/or topical corticosteroids)
Grade 2	May maintain dose level, but initiate/intensify appropriate skin toxicity therapy (such as antihistamines and/or topical corticosteroids).
Grade 3, despite skin toxicity therapy	Recommendation: Omit dose until resolved to Grade ≤ 1, then: If resolved resolved in ≤ 7 days, then maintain dose level If resolved resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue subject from study drug treatment (mandatory)
Grade 4, despite skin toxicity therapy	Mandatory: Discontinue subject from study drug treament
Fatigue/ Asthenia (General disorders and administration site conditions)	
Grade 1 or 2	May maintain dose level
Grade 3	Recommendation: Omit dose until resolved to ≤ grade 1, then : If resolved in ≤ 14 days, then maintain dose level If resolved in > 14 days, then discontinue subject from study drug treatment (mandatory)
Other adverse events	
Grade 1 or 2	May maintain dose level
Grade 3	Recommendation: Omit dose until resolved to ≤ grade 1, maintain dose level
Grade 4, except alopecia	Recommendation: Discontinue from study drug treatment

[redacted]

Dose Schedule modifications for Canakinumab[a]	
Worst toxicity *CTCAE Version 5.0 during a cycle of therapy*	
All dose modifications should be based on the worst preceding toxicity. *[a] Common Toxicity Criteria for Adverse Events (CTCAE Version 5.0)* *[b] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.)* *[c] "Concomitant" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold* *If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment at the same dose* *[d] The subject should be monitored biweekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.* *Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury*	

[redacted]

6.3.2 Dose adjustments for QTcF prolongation

In case of QTcF >500 msec, (or QTcF prolongation >60 msec from baseline)

1. Assess the quality of the ECG recording and the QT value and repeat if needed
2. Determine serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
3. Review concomitant medication associated with QT prolongation, including drugs with a "Known", "Possible", or "Conditional risk of Torsades de Pointes, and drugs with the potential to increase the risk of study drug exposure related QT prolongation
4. Check study drug dosing schedule and treatment compliance
5. Consider collecting a time-matched PK, and record time and date of last study drug intake.

After confirming ECG reading at site, if QTcF > 500 msec

- Interrupt study treatment
- Repeat ECG and confirm ECG diagnosis by a cardiologist
- If QTcF confirmed > 500 msec:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify and address clinical conditions that could potentially prolong the QT as per the ECG and QTc Clinical Safety Standards Guidelines Section 3.3.1.
  - Consult with a cardiologist (or qualified specialist)
  - Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 msec.
- After resolution to ≤ 480 msec, consider re-introducing treatment, and increase ECG monitoring for the next treatment(s):
  - If QTcF remains ≤ 500 msec after re-introducing treatment, continue planned ECG monitoring during subsequent treatment
  - If QTcF recurs > 500 msec after re-introducing treatment, discontinue subject from study treatment.

6.3.3 Follow-up for toxicities

6.3.3.1 Follow up for infections

Subjects should be followed closely for any signs or symptoms of infection and receive prompt appropriate treatment for any suspected infection.

6.3.3.2 Follow up on potential drug-induced liver injury (DILI) cases

DILI Diagnosis

Subjects with elevated transaminases combined with an increase in total bilirubin (TBIL) may be indicative of potentially severe DILI. These events should therefore be considered as clinically important and should be assessed appropriately to establish the cause of the abnormal liver function. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

[redacted]

The threshold for potential DILI may depend on the subject's baseline AST/ALT and TBIL value (Table 6-2 in Section 6.3.1); subjects meeting any of the following criteria will require further follow-up and assessments as outlined below:

- For subjects with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For subjects with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline] or 8 x ULN, whichever is lower combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before the diagnosis of DILI is confirmed.

Hepatic toxicity monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin, direct and indirect bilirubin, alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), creatine kinase, prothrombin time (PT) or international normalized ratio (INR) and gamma-glutamyltransferase (GGT). For subjects with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only.

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion – CT, MRI, duplex sonography.

Perform relevant examinations (Ultrasound or MRI, ERCP) as appropriate, to rule out if LFTs are caused by cholestasis (defined as ALP elevation > 2.0 x ULN with R value < 2 in subjects without bone metastasis, or elevation of ALP liver fraction in subjects with bone metastasis).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury.

Table 6-3 provides guidance on specific clinical and diagnostic assessments to be (OR which can be) performed locally to rule out possible alternative causes of the observed LFT abnormalities.

Table 6-3 Clinical and diagnostic assessments for observed LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronicCHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

[redacted]

Other causes should also be considered based upon subject's medical history (Hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; CVD / Ischemic hepatitis – ECG, prior hypotensive episodes; T1D / glycogenic hepatitis).

Following appropriate causality assessments, as outlined above, the causality of the drug is estimated as "probable" i.e. >50% likely, if it appears greater than all other possible causes of liver injury combined. The term "drug-induced" indicates *probably caused* by the drug, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

DILI Management

In the absence of cholestasis, these subjects should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2 . A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug to determine exposure to study drug if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases of DILI confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, met the definition of SAE (Section 8.2.1) and must be reported as SAE using the term "potential drug-induced liver injury". All events must be followed up with the outcome clearly documented. Results of tests as well as other clinically important information will be recorded in the eCRF.

6.4 Concomitant medications

The investigator should instruct the subject to notify the study site about any new medications he/she takes after signing the informed consent. All medications including supplements and herbal/natural medications, surgeries, and significant non-drug therapies (including physical therapy and blood transfusions) taken within 30 days of screening and administered after the subject has signed informed consent must be listed on the appropriate eCRF.

For any antineoplastic therapy, surgery, or radiotherapy initiated after the start of study treatment, the reason for its use must be clearly documented and cancer recurrence must be assessed and documented.

[redacted]

Prior treatment for TB infection should be listed on the eCRF. Influenza vaccines administered two years prior to study start and pneumococcal vaccines administered five years prior to study start should be recorded on the eCRF. Vaccinations taken during the trial should also be reported on the eCRF. Subjects must be discontinued from the trial if administered any live and attenuated vaccines during the course of the study (see Section 6.4.2).

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

Drug-drug interaction potential

No formal drug-drug interaction studies have been conducted with canakinumab. Elimination pathways for IgG type monoclonal antibodies such as canakinumab are distinct from metabolic pathways of small molecules. The IgG-based molecules are cleared from the body by a combination of processes such as proteolysis by the liver, elimination by the Reticuloendothelial System and nonspecific endocytosis, whereas small molecular weight drugs are typically eliminated through CYP450-mediated oxidation pathways and are therefore not expected to affect the pharmacokinetics of canakinumab. The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as IL-1β. Thus, CYP450 expression may be normalized when potent cytokine inhibitory therapy, such as canakinumab is introduced.

6.4.1 Permitted concomitant therapy

Potential drug interactions between study drug and concomitant medications should always be taken into consideration.

6.4.2 Prohibited concomitant therapy

6.4.2.1 Immunosuppressants

Use of any treatments below is NOT allowed after the start of study treatment due to potential increase in immunosuppressant related concomitant conditions. They are prohibited for the duration of the study and for at least 130 days after discontinuation of study treatment.

If a subject chooses to continue one of the medications below, they would still be required to be followed as per protocol to assess for NSCLC disease recurrence.

- Any anti retro-virals and / or any biologic drugs targeting the immune system (e.g., TNFα blockers, anakinra, rituximab, abatacept, tocilizumab)
- immune modulating agent in doses with systemic effects e.g.:
  i. Prednisone >20 mg (or equivalent) oral or intravenous daily for >14 days;
  ii. Prednisone > 5 mg and ≤ 20 mg (or equivalent) daily for > 30 days;
  iii. Equivalent dose of methotrexate >15 mg weekly.
- Live or attenuated vaccines within 90 days of study treatment and after initiation of study drug. Subjects must be discontinued from the trial if administered any live or attenuated vaccine during the course of the study.

[redacted]

6.4.2.2 Other anti-cancer therapy

Anti-cancer therapy (chemotherapy, targeted therapy, biologic therapy, radiation therapy, and anti-cancer surgery) other than the study treatment must not be given to subjects during the treatment phase of the study. If such agents are required then the subjects must be permanently discontinued from the study drug and evaluation of NSCLC disease recurrence must be performed. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type and hormonal maintenance for breast and prostate cancer >3 years.

6.5 Subject numbering, treatment assignment or randomization

6.5.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available to the investigator through the Clinical Data Management interface.

The investigator or designated staff will contact the Interactive Response Technology (IRT) and provide the requested identifying information for the subject to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed. If the subject fails to be randomized or start treatment for any reason, the reason will be entered into the disposition page. IRT must be notified within 2 days that the subject was not randomized.

Applicable for sub-study:

Each subject is identified in the sub-study by a Subject Number (Subject No.) that is assigned when the subject is first enrolled into sub-study. This number will be different from the subject number given if subject enrolls into the main study.

If subjects from sub-study enroll into the main study, both subject IDs will be linked and subjects will continue with subject ID provided in main study. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it so that each subject is numbered uniquely across the entire database.

6.5.2 Treatment assignment or randomization

Randomization will be performed using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. Random permuted blocks scheme will be used for this study.

A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment

[redacted]

groups to randomization numbers in the specified ratio. The randomization list will be reviewed by a Biostatistics Quality Assurance Group and locked by them after approval.

Prior to dosing, all subjects who fulfill all inclusion/exclusion criteria will be assigned the lowest available number on the randomization list.

Subjects will be assigned to one of the two treatment arms (Section 4.1 and Section 6.1) in a ratio of 1:1. Randomization will be stratified by:

- AJCC/UICC v.8 stage: IIA vs. IIB vs. IIIA vs. IIIB with T>5cm, N2 disease
- Histology: squamous versus non-squamous
- Region: Western Europe and North America vs. eastern Asia vs. Rest of the world (RoW)

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

Prior to dosing, all subjects who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will log on to the IRT and confirm that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject. The randomization number will not be communicated to the site staff.

6.5.3 Treatment blinding

This is a double blind study. In particular, subjects, investigators, study team, or anyone involved in the study conduct will remain blinded to the identity of the treatment from the time of randomization until unblinding of the study.

Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible to anyone involved in the conduct of the study, with the exception of the external independent statistical group, which needs to prepare safety interim DFS analysis reports for the DMC, the PK bioanalyst, modeler and modeling programmer. These personnel will not be involved in any other trial activities and treatment allocation information will be kept confidential until clinical database lock. The study bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the samples. The identity of the treatments will be concealed by the use of investigational drugs (canakinumab or placebo) that are identical in packaging, labeling, schedule of administration and in appearance. Confidentiality of randomization data is required to limit the occurrence of potential bias arising from the influence that the knowledge of treatment may have on the recruitment and allocation of subjects. Unblinding will only occur in the case of subject emergencies (see Section 8.3),

[redacted]

following the Data Monitoring Committee (DMC) recommendations (e.g. after the interim analyses) (see Section 10.7), for regulatory reporting purposes and at the end of the study.

[redacted]

An independent statistical group (external to and independent of Novartis), not involved in the trial conduct, will prepare data reports for the DMC. Details will be presented in the DMC charter (see Section 8.6).

6.6 Study drug preparation and dispensation

Each study site will be supplied by Novartis with study treatment in packaging of identical appearance per product volume. For allocation of the study medication, IRT will be used by the site personnel at the Investigator's site.

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

Appropriate documentation of the subject specific dispensing process must be maintained.

Study drug will be administered as a subcutaneous injection by appropriately trained study center personnel.

Following the first dose on Cycle 1 Day 1, subsequent doses will be on Day 1 of every 21-day cycle for 18 cycles. The treatment visits must occur within ±3 days of the target date.

All dosages prescribed and dispensed to the subject and all dose interruptions during the study must be recorded on the appropriate eCRF.

Giving the injection

All injections must be administered by the site staff only.

1. Choose an injection site on the upper arm, upper thigh, or abdomen. Do not use an area that has a rash or broken skin, or is bruised or lumpy. Avoid injecting into scar tissue- as this may lead to insufficient exposure to canakinumab. Avoid injecting into a vein.
2. Clean the injection site with a new alcohol swab. Allow the area to dry. Uncap the injection needle.
3. Gently pinch the skin up at the injection site. Hold the syringe at an approximately 45-degree angle and in a single, smooth motion, push the needle completely into the skin.
4. Keep the needle all the way in the skin while slowly pushing the syringe plunger down until the barrel is empty. Release the pinched skin and pull the needle straight out. Dispose of the needle and syringe in the sharps container without recapping or removing the needle.

[redacted]

5. After the injection: Do not rub the injection area. If bleeding occurs, apply a clean, dry cotton swab over the area, and press gently for 1 to 2 minutes, or until bleeding stops. Then apply an adhesive bandage.

6.6.1 Study treatment packaging and labeling

Study treatment, canakinumab, will be provided as global clinical blinded supply and will be packed and labeled under the responsibility of Novartis, Drug Supply Management.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to study treatment and strength).

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the [canakinumab Investigator's Brochure].

Upon receipt, all study treatment should be stored in the refrigerator at 2-8 degrees C (36-46 degrees F, do not freeze) and protected from light. Study treatment temperature should be verified and documented daily (business days) with a minimal / maximum thermometer or another equivalent temperature recording tool. Clinical supplies are to be dispensed only in accordance with the protocol.

Table 6-4 Supply and storage of study treatments

Study treatments	Supply	Storage
Canakinumab or placebo	Centrally supplied by Novartis	Refrigerate at 2-8 degrees C (36-46 degrees F), Do not freeze and protect from light.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Study treatment will be administered at the clinic by the investigative staff with the dosing record captured within each visit on the appropriate eCRF.

Compliance will be assessed by the investigator and/or study personnel at each subject visit and information provided by the subject and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each subject visit.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site or remote monitoring visits and at the completion of the study.

[redacted]

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the Investigator must not destroy any drug labels, or any partly used or unused drug supply.

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

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility or third party, as appropriate, or locally at the site only if permitted by local regulations and authorized by Novartis.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. Each treatment cycle is 21 days (the 21 day cycle length is fixed regardless of whether the dose of canakinumab is withheld). All visits are to be scheduled according to the appropriate number of calendar days from study drug administration on Cycle 1 Day 1. A visit window of +/- 1 day in Cycle 1 and +/- 3 days in Cycle 2 onwards through EOT and Safety follow up is allowed. For Post treatment surveillance and Survival follow up, visit windows of ± 7 days will apply in years 2 and 3, and visit windows of ± 21 days for years 4 and 5. Imaging evaluations may be performed ± 14 days of the due date of the assessment during years 1-3 and ± 21 days in years 4 and 5. **Note: If treatment with canakinumab/placebo is withheld or discontinued at any time during the study, all study visits, safety and efficacy assessments should continue according to the appropriate number of calendar days from Cycle 1 Day 1 as per the schedule of assessments.**

Imaging assessments are to continue regardless of starting a new antineoplastic therapy after discontinuation of study treatment, if the patient has not progressed from their NSCLC or been diagnosed with new lung primary. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects who discontinue from study treatment are to return for the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule

Subjects who discontinue study treatment before completing the study, and those who 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 will be performed.

As per Section 2.7, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative

[redacted]

methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 7-2 provides details on the assessments to be performed for the sub-study.

[redacted]

Table 7-1 Visit evaluation schedule (main study, CACZ885T2301)

	Protocol Section	Screening Phase	Treatment Phase Canakinumab / placebo (18 cycles / 54 weeks)										Post treatment surveillance (PTS)		Follow up phase
Visit Name		**Screening**	**Cycle 1**			**Cycles 2 to 17**	**C18/ EOT**	**Safety follow up (every 28d for 130d)**					**Post treatment surveillance**		**Survival follow up**
Study/treatment cycle day		**-28 to -1**	**C1D1**	**C1D8**	**C1D15**	**C2D1, C3D1, etc.**	**C18/EOT**	**Safety 1**	**Safety 2**	**Safety 3**	**Safety 4**	**Safety 5**	**Years 2 and 3**	**Years 4 and 5**	**Every 12 weeks**
Visit Number		1	110	140	150	210, 310, etc.	1999	2010	2020	2030	2040	2050	3010, 3020, 3030, 3040 etc.	3050 3060	SS
Obtain Study Informed Consent	7.1.2	X													
[redacted]															
IRT Screening (after ICF)	7.1.2	S													
Study Disposition Form	7.1.4	Completed upon end of study treatment or when a subject exits the study for any reason (X)													
Demography	7.1.2.3	X													
Inclusion/exclusion criteria	5.2, 5.3	X													
Medical history	7.1.2.3	X													
Smoking history	7.1.2.3	X													
Diagnosis, stage and grade of cancer	7.1.2.3	X													

[redacted]

	Protocol Section	Screening Phase	Treatment Phase Canakinumab / placebo (18 cycles / 54 weeks)										Post treatment surveillance (PTS)		Follow up phase
Visit Name		**Screening**	**Cycle 1**			**Cycles 2 to 17**	**C18/ EOT**	**Safety follow up (every 28d for 130d)**					**Post treatment surveillance**		**Survival follow up**
Study/treatment cycle day		**-28 to -1**	**C1D1**	**C1D8**	**C1D15**	**C2D1, C3D1, etc.**	**C18/EOT**	**Safety 1**	**Safety 2**	**Safety 3**	**Safety 4**	**Safety 5**	**Years 2 and 3**	**Years 4 and 5**	**Every 12 weeks**
Visit Number		1	110	140	150	210, 310, etc.	1999	2010	2020	2030	2040	2050	3010, 3020, 3030, 3040 etc.	3050 3060	SS
Collection of concomitant molecular alteration data	7.1.2.3	X													
[redacted]															
Prior anti-neoplastic therapies (medication, surgery, radiotherapy)	7.1.2.3	X													
[redacted]															
Prior/concomitant medications	7.1.2.3	Continuous, up to 130 days after the EOT visit. (X)													

[redacted]

	Protocol Section	**Screening Phase**	**Treatment Phase Canakinumab / placebo (18 cycles / 54 weeks)**										**Post treatment surveillance (PTS)**		**Follow up phase**
Visit Name		**Screening**	**Cycle 1**			**Cycles 2 to 17**	**C18/ EOT**	**Safety follow up (every 28d for 130d)**					**Post treatment surveillance**		**Survival follow up**
Study/treatment cycle day		**-28 to -1**	**C1D1**	**C1D8**	**C1D15**	**C2D1, C3D1, etc.**	**C18/EOT**	**Safety 1**	**Safety 2**	**Safety 3**	**Safety 4**	**Safety 5**	**Years 2 and 3**	**Years 4 and 5**	**Every 12 weeks**
Visit Number		1	110	140	150	210, 310, etc.	1999	2010	2020	2030	2040	2050	3010, 3020, 3030, 3040 etc.	3050 3060	SS
Eligibility checklist (within IRT)	7.1.2.1		S												
IRT Randomization	6.5.2		X												
IRT study drug dispensation	6.6		S			S (every cycle)	S								
Physical examination	7.2.2.2	S	S			S	S	S	S	S	S	S	Every 26 weeks (S)	Annually (S)	
ECOG Performance status	7.2.2.5	X	X			X	X	X	X	X	X	X	Every 26 weeks (X)	Annually (X)	
Vital signs	7.2.2.3	X	X			X	X	X	X	X	X	X	Every 26 weeks (X)	Annually (X)	
Weight	7.2.2.4	X	X			X	X	X	X	X	X	X	Every 26 weeks (X)	Annually (X)	
Height	7.2.2.4	X													

[redacted]

	Protocol Section	Screening Phase	Treatment Phase Canakinumab / placebo (18 cycles / 54 weeks)										Post treatment surveillance (PTS)		Follow up phase
Visit Name		**Screening**	**Cycle 1**			**Cycles 2 to 17**	**C18/ EOT**	**Safety follow up (every 28d for 130d)**					**Post treatment surveillance**		**Survival follow up**
Study/treatment cycle day		**-28 to -1**	**C1D1**	**C1D8**	**C1D15**	**C2D1, C3D1, etc.**	**C18/EOT**	**Safety 1**	**Safety 2**	**Safety 3**	**Safety 4**	**Safety 5**	**Years 2 and 3**	**Years 4 and 5**	**Every 12 weeks**
Visit Number		1	110	140	150	210, 310, etc.	1999	2010	2020	2030	2040	2050	3010, 3020, 3030, 3040 etc.	3050 3060	SS
EORTC QLQ-C30 with lung module QLQ-LC13 incorporated	7.2.6	X	(Prior to administration of investigational product or any other procedures). After randomization every 3 weeks for 18 cycles, at EOT, every 4 weeks during the 130-day safety follow up, every visit before any radiological study is done, before any unscheduled imaging assessments and two follow up visits after documented NSCLC disease recurrence (one within 7 days and one within 28 days after discussing disease recurrence with the subjects). (X)												
EQ-5D-5L	7.2.6	X													
Determination of tuberculosis status	7.2.2.1	X													
HIV screen, HBsAg and HCV Antibody (For Japan only- in Japan, HBc antibody and HBs antibody are additionally included)	7.2.2.6	X													
[redacted]															
Hematology	7.2.2.6.1	X	X			X	X	X	X	X	X	X			

[redacted]

	Protocol Section	Screening Phase	Treatment Phase Canakinumab / placebo (18 cycles / 54 weeks)										Post treatment surveillance (PTS)		Follow up phase
Visit Name		**Screening**	**Cycle 1**			**Cycles 2 to 17**	**C18/ EOT**	**Safety follow up (every 28d for 130d)**					**Post treatment surveillance**		**Survival follow up**
Study/treatment cycle day		**-28 to -1**	**C1D1**	**C1D8**	**C1D15**	**C2D1, C3D1, etc.**	**C18/EOT**	**Safety 1**	**Safety 2**	**Safety 3**	**Safety 4**	**Safety 5**	**Years 2 and 3**	**Years 4 and 5**	**Every 12 weeks**
Visit Number		1	110	140	150	210, 310, etc.	1999	2010	2020	2030	2040	2050	3010, 3020, 3030, 3040 etc.	3050 3060	SS
Biochemistry	7.2.2.6.2	X	X			X	X	X	X	X	X	X			
Coagulation	7.2.2.6.4	X	As clinically indicated (X)												
Urinalysis	7.2.2.6.5	X	X			X	X	X	X	X	X	X			
Serum pregnancy test	7.2.2.6.6	X					X								
Urine pregnancy test (for women of child bearing potential only)	7.2.2.6.6		S			S		S	S	S	S	S			
CT scan or MRI with contrast of chest, abdomen and pelvis	7.2.1	X	Every 12 weeks (every 4 cycles) for the first year, every 26 weeks years 2 and 3, and then annually years 4 and 5 (X)												
CT or MRI chest and abdomen (including full liver and bilateral adrenal imaging) low-dose non-contrast (contrast may be added at investigator's discretion)	7.2.1													Annually (X)	
Whole body bone scan	7.2.1	As clinically indicated (X)													

[redacted]

	Protocol Section	Screening Phase	Treatment Phase Canakinumab / placebo (18 cycles / 54 weeks)										Post treatment surveillance (PTS)		Follow up phase
Visit Name		**Screening**	**Cycle 1**			**Cycles 2 to 17**	**C18/ EOT**	**Safety follow up (every 28d for 130d)**					**Post treatment surveillance**		**Survival follow up**
Study/treatment cycle day		**-28 to -1**	**C1D1**	**C1D8**	**C1D15**	**C2D1, C3D1, etc.**	**C18/EOT**	**Safety 1**	**Safety 2**	**Safety 3**	**Safety 4**	**Safety 5**	**Years 2 and 3**	**Years 4 and 5**	**Every 12 weeks**
Visit Number		1	110	140	150	210, 310, etc.	1999	2010	2020	2030	2040	2050	3010, 3020, 3030, 3040 etc.	3050 3060	SS
MRI of brain	7.2.1	X	As clinically indicated (X)												
Newly obtained biopsy for confirmation of disease recurrence	7.2.4.1.2		At the time of initial disease recurrence if radiological evidence is not conclusive (X)												
Single ECG (standard 12-lead)	7.2.2.7	X	As clinically indicated (X)												
Adverse events	8.1	X	Continuous, up to 130 days after EOT (X)										SAEs related to study treatment (X)		
Immunogenicity (IG) (Anti-canakinumab Ab)	7.2.3.1		X			X – C2D1 C4D1 C6D1 C9D1 C12D1	X	X		X		X			

[redacted]

	Protocol Section	Screening Phase	Treatment Phase Canakinumab / placebo (18 cycles / 54 weeks)										Post treatment surveillance (PTS)		Follow up phase
Visit Name		**Screening**	**Cycle 1**			**Cycles 2 to 17**	**C18/ EOT**	**Safety follow up (every 28d for 130d)**					**Post treatment surveillance**		**Survival follow up**
Study/treatment cycle day		**-28 to -1**	**C1D1**	**C1D8**	**C1D15**	**C2D1, C3D1, etc.**	**C18/EOT**	**Safety 1**	**Safety 2**	**Safety 3**	**Safety 4**	**Safety 5**	**Years 2 and 3**	**Years 4 and 5**	**Every 12 weeks**
Visit Number		1	110	140	150	210, 310, etc.	1999	2010	2020	2030	2040	2050	3010, 3020, 3030, 3040 etc.	3050 3060	SS
PK	7.2.3.1		X	X	X	X – C2D1 C4D1 C6D1 C9D1 C12D1	X	X	X	X	X	X			
IL-1β (PD)	7.2.3.1		X		X	X – C4D1 C12D1	X	X		X		X			
[redacted]															

[redacted]

	Protocol Section	Screening Phase	Treatment Phase Canakinumab / placebo (18 cycles / 54 weeks)											Post treatment surveillance (PTS)		Follow up phase
Visit Name		**Screening**	**Cycle 1**			**Cycles 2 to 17**	**C18/ EOT**	**Safety follow up (every 28d for 130d)**						**Post treatment surveillance**		**Survival follow up**
Study/treatment cycle day		**-28 to -1**	**C1D1**	**C1D8**	**C1D15**	**C2D1, C3D1, etc.**	**C18/EOT**	**Safety 1**	**Safety 2**	**Safety 3**	**Safety 4**	**Safety 5**		**Years 2 and 3**	**Years 4 and 5**	**Every 12 weeks**
Visit Number		1	110	140	150	210, 310, etc.	1999	2010	2020	2030	2040	2050		3010, 3020, 3030, 3040 etc.	3050 3060	SS
[redacted]																
canakinumab/ placebo	6.6		Every 3 weeks for 18 cycles (54 weeks) (X)													
Non-drug therapies and procedures	8.1.1 10.3		Continuous (X)													
IRT Discontinuation canakinumab / placebo	7.1.4						S									
Subsequent anti-neoplastic therapies (medication, surgery, radiotherapy)	7.1.6						X	X	X	X	X	X		X	X	X

[redacted]

	Protocol Section	Screening Phase	Treatment Phase Canakinumab / placebo (18 cycles / 54 weeks)										Post treatment surveillance (PTS)		Follow up phase
Visit Name		**Screening**	**Cycle 1**			**Cycles 2 to 17**	**C18/ EOT**	**Safety follow up (every 28d for 130d)**					**Post treatment surveillance**		**Survival follow up**
Study/treatment cycle day		**-28 to -1**	**C1D1**	**C1D8**	**C1D15**	**C2D1, C3D1, etc.**	**C18/EOT**	**Safety 1**	**Safety 2**	**Safety 3**	**Safety 4**	**Safety 5**	**Years 2 and 3**	**Years 4 and 5**	**Every 12 weeks**
Visit Number		1	110	140	150	210, 310, etc.	1999	2010	2020	2030	2040	2050	3010, 3020, 3030, 3040 etc.	3050 3060	SS
Survival Follow-up	7.1.6.2														X

X = assessment to be recorded in the clinical database or received electronically from a vendor
S = assessment to be recorded in the source documentation only
SS = Survival Status

[redacted]

[redacted]

Table 7-2 Sub-study visit evaluation schedule (CACZ885T2301A)****

Visit	Volume	Protocol Section	Confirm eligibility*	Pre- resection surgery collection**	Post resection surgery collection***
Obtain Sub-study Informed Consent	N/A	7.1.2.4	X		
Inclusion criteria for sub-study	N/A	5.2.1	X		
Serious Adverse Events related to sub-study blood collection	N/A	8.2.2		X	X
Biomarker sub-study collections:					
Blood (serum) for hs-CRP testing at central laboratory	5 mL	7.2.4.2		X	X
Blood (plasma) for cytokine panel testing	10 mL	7.2.4.2		X	X
Blood (plasma) for ctDNA	20 mL	7.2.4.2		X	

X = assessment to be recorded in the clinical database or received electronically from a vendor

*Eligibility confirmation can occur on the same day as the pre- resection surgery sample collection.

**Either one day prior to, or on the day of resection surgery.

***Prior to first administration of chemotherapy, not before 30 days after surgery but within 70 days after surgery. For pathological stages not requiring chemotherapy, these samples must be drawn prior to their first imaging performed since resection surgery, still within 70 days after surgery.

****For China only: biomarker collection is conditional upon approval from HA, EC and additional authorities (i.e. HGRAC).

[redacted]

7.1.1 Molecular pre-screening

Not applicable

7.1.2 Screening

Written informed consent must be obtained before any study specific procedure is performed.

Subjects may be screened after undergoing complete surgical resection of their NSCLC and having R0 status confirmed (negative margins on pathologic review), after completing adjuvant cisplatin-based doublet chemotherapy if applicable, (and, if applicable, radiation therapy is allowed if indicated as per local guidelines or practice) and after all entry criteria are met. Subjects must not have had preoperative neo-adjuvant chemotherapy or radiotherapy to achieve the R0 status.

After signing the study ICF, the screening assessments will be done within 1 to 28 days prior to randomization (see Table 7-1 for list of assessments to be performed). Laboratory parameters may be retested within the 28-day screening window (day -28 to day -1) period for an individual subject if such parameters meet an exclusion criterion when initially tested. Laboratory assessments performed as part of the screening evaluations will not be required to be repeated prior to dosing (except urine pregnancy test) unless deemed clinically necessary by investigator and/or required as per local institutional policies. Tumor imaging assessments will be performed at screening between Day -28 and Day -1. For details of assessments, see Table 7-1.

Assessments of patient reported outcomes during the screening period should be collected prior to any clinical assessments, drug dosing or diagnostic testing.

Imaging assessments will be performed at screening between Day -28 and Day -1. Imaging assessments already completed during the regular work-up of the subject within 28 days prior to start of treatment, including before signing the main study ICF can be considered as the baseline images for this study. Any imaging assessments obtained after randomization cannot be considered baseline images.

A new ICF will need to be signed if the investigator chooses to re-screen the subject after a subject has screen failed. In case of re-screening, the same subject ID will be used. All required screening activities must be performed when the subject is rescreened for participation in the study. An individual subject may only be re-screened once for the study. Details on capturing re-screening will be outlined in the eCRF Completion Guidelines.

Sub-study participants:

Written informed consent must be obtained prior to participation in the sub-study.

Subjects may be assessed for eligibility into the sub-study if they have NSCLC Stage IIA-IIIA, IIIB (T>5cm, N2 disease only) and who are candidates for complete resection surgery (and therefore prospective candidates for the main study, CACZ885T2301). After signing the sub-study ICF, and sub-study eligibility criteria are met, biomarker samples will be collected as per Table 7-2.

[redacted]

7.1.2.1 Eligibility screening

Following registering in the IRT for screening, subject eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Allocation to one of the two study arms will also be registered via IRT. Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 Information to be collected on screening failures

A subject who signs the main informed consent but fails to satisfy all eligibility criteria for any reason will be considered a screen failure. The reason for not satisfying eligibility criteria and not being enrolled will be entered on the disposition eCRF. The following eCRFs must be completed for screen failure subjects:

- Date of visit
- Demographics
- Informed Consent
- Study Disposition Form
- Inclusion/ Exclusion criteria
- Death (if applicable)
- Withdrawal of consent (if applicable)
- SAEs (if related to reasons for screen failure)

No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). If the subject fails to be enrolled, the IRT must be notified within 2 days of the screen fail that the subject was not enrolled.

7.1.2.3 Subject demographics and other baseline characteristics

Data to be collected on subject characteristics at screening include:

- Demography (including: age, gender, race and ethnicity, or as allowed by local regulations)
- Relevant medical history
- History of smoking
- NSCLC diagnosis and extent of disease, including:
  - Date of diagnosis of NSCLC
  - Site of disease
  - Characteristics of disease including stage and histology
  - Concomitant molecular alteration when available (and results of all the tests performed even if wild type)
  - Surgical and pathology reports confirming negative margins
- Prior antineoplastic therapies (medications, radiation, surgeries)
- Prior and Concomitant Medications, surgical and medical procedures

[redacted]

7.1.2.4 Information to be collected on sub-study participants

The following eCRFs must be completed for sub-study subjects:

- Date of visit
- Demography (including: age, gender, race and ethnicity, or as allowed by local regulations)
- Informed Consent
- Study Disposition Form
- Inclusion criteria
- Sub-study sample collection
- Death (if applicable)
- Withdrawal of consent (if applicable)
- SAEs (only if related to reasons for sub-study blood collection)

7.1.3 Treatment period

The study treatment phase begins on Cycle 1 Day 1 with the first administration of canakinumab/placebo. Subjects will continue their assigned treatment until they complete 18 cycles or experience any one of the following: disease recurrence as determined by the investigator, unacceptable toxicity that precludes further treatment, treatment discontinuation at the discretion of the Investigator or subject, or start of a new antineoplastic therapy, or death, or lost to follow-up, whichever occurs first. Subjects will be assessed as per visit schedule in Table 7-1. All subjects will be followed for AEs and SAEs for at least 130 days following the EOT visit. Subjects will present to the clinical site every 28 days, for a total of five follow-up visits. If disease recurrence is not observed during the treatment phase, subjects will be followed for recurrence during the post treatment surveillance phase for up to five years (see Section 7.2.1).

Visit windows of ± 1 calendar day will be applicable to scheduled study assessments during Cycle 1. Visit windows of ± 3 days from scheduled study assessments during the treatment phase will apply during and beyond Cycle 2 through EOT and Safety follow up visits. For Survival follow up and Post treatment surveillance, visit windows of ± 7 days will apply in years 2 and 3, and visit windows of ± 21 days will apply for years 4 and 5. Imaging assessments will have a ± 14 day window during years 1-3, and ± 21 days in years 4 and 5. For details of assessments, refer to Table 7-1.

7.1.4 Discontinuation of study treatment

Subjects who discontinue study treatment should NOT automatically be considered withdrawn from the study. See Table 7-1 for the required assessments of these subjects after discontinuation of study treatment. Subjects who discontinue study treatment during the treatment phase should be scheduled for a visit within 7 days or as soon as possible after the last dose of study treatment, at which time all of the assessments listed for the EOT visit will be performed. If a subject withdraws from treatment at a study visit, EOT assessments that are already part of that scheduled study visit do not need to be repeated. The disposition page should be completed, giving the date and reason for stopping treatment.

[redacted]

For subjects who discontinue treatment for reasons other than documented disease recurrence, initiation of new antineoplastic therapies, death, lost to follow-up, or withdrawal of consent, assessments must continue to be performed according to Table 7-1 until disease recurrence, withdrawal of consent by the subject, subject is lost to follow up, death or the sponsor terminates the study for up to five years.

Subjects may voluntarily discontinue from the study for any reason at any time. If a subject decides to discontinue from the study, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the subject's chart and on the appropriate eCRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

At a minimum, all subjects who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 130 days following the EOT visit (see Section 7.1.6.1).

The investigator may discontinue study treatment for a given subject if, he/she believes that continuation would be detrimental to the subject's well-being.

In addition to mandatory study drug discontinuation criteria listed in Table 6-2, treatment must also be discontinued under the following circumstances:

- Pregnancy
- Study Terminated by Sponsor
- Subject/guardian decision
- Physician decision
- Non-compliance, as defined by missing any single dose greater than 42 days from the intended day of the next scheduled dose.
- Initiation of a new antineoplastic therapy

Subjects who become pregnant during the trial must be withdrawn (Section 8.4). Subjects who become pregnant must cease all tumor assessments regardless of whether or not they developed recurrence.

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

Discontinuation from study is when the subject permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the subject agrees, a final evaluation at the time of the subject's study discontinuation should be made as detailed in the assessment table (refer to Table 7-1).

7.1.4.1 Replacement policy

Not applicable

[redacted]

7.1.5 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information. Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the subject therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study informational research research results (data) that have already been collected for the study evaluation, (including processing of biological samples that has already started at time of consent any data resulting from the analysis of a subject's samples until their time of withdrawal/opposition.) according to applicable law. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

Applicable for sub-study:

Subjects may voluntarily withdraw consent/ to participate in the sub-study for any reason at any time. Withdrawal of consent occurs only when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation,All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

[redacted]

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements

7.1.6 Follow up evaluations

7.1.6.1 Safety follow up

All subjects will be followed for AEs and SAEs for at least 130 days following the EOT visit. Subjects will present to the clinical site every 28 days, for a total of five follow-up visits (see Table 7-1). At the end of this period, the investigator should assess and discuss with the subject any AEs observed and concomitant medications taken since discontinuation of study treatment. Subjects whose treatment is permanently discontinued due to an AE (clinical or based on abnormal laboratory value) must be followed until resolution or stabilization of the event, whichever comes first. In case of an abnormal laboratory value, blood tests should be repeated until resolution or stabilization.

If a new antineoplastic therapy is initiated after discontinuation of study treatment, only SAEs suspected to be related to study treatment will be collected in the Adverse Events eCRF.

7.1.6.2 Survival

All subjects who discontinue from the study treatment will be followed up every 12 weeks for survival until the final overall survival (OS) analysis or death, lost to follow-up or withdrawal of consent for survival follow-up (see Table 7-1). Additional survival assessments may be performed outside the 12 weeks follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs. The investigator or his designee will collect this survival information and any new anti-neoplastic therapies for all subjects until the final survival analysis. Follow-up can be done via a phone contact.

7.1.7 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits, or fail to respond to any site attempts to contact them, without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other subject's data privacy rights), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered lost to follow-up until due diligence has been completed. Subjects lost to follow up should be recorded as such on the appropriate disposition eCRF.

7.2 Assessment types

7.2.1 Recurrence assessments

Detection of first disease recurrence will be done by clinical evaluation that includes physical examination and radiological tumor measurements as determined by the investigator. In case of non-conclusive radiological evidence, a biopsy should be performed to confirm recurrence.

[redacted]

If a biopsy is performed, the fresh tissue sample and the pathology report should be submitted to the central lab.

The following assessments are required at screening/baseline:

- Chest, abdomen and pelvis CT or MRI
- Brain MRI
- Whole body bone scan, if clinically indicated

Subsequent imaging assessments will be done every 12 weeks for the first year (treatment phase) following Cycle 1 Day 1, then every 26 weeks during years two and three, and annually during years four and five (post-treatment surveillance phase) (see Table 7-1). **The intervals between imaging assessments across all study phases should be respected as described above regardless of whether study treatment is temporarily withheld or permanently discontinued before the last scheduled dose administration on Cycle 18 Day 1, or if unscheduled assessments are performed.** A window of ±14 days in years 1-3, then ±21 days in years 4 and 5 is permitted to take into account scheduling over holidays.

First disease recurrence must be radiologically confirmed by the investigator. In case of non-conclusive radiological evidence, a biopsy should be performed to confirm recurrence. If a biopsy is not feasible, the subject will be followed up until recurrence can be confirmed as per protocol (radiologically conclusive and/or biopsy).

For any antineoplastic therapy, surgery, or radiotherapy initiated after the start of study treatment, the reason for its use must be clearly documented and recurrence of cancer must be assessed and documented. Imaging assessments are to continue regardless of start of new antineoplastic therapies.

If a subject discontinues study treatment for reasons other than recurrence, recurrence assessments should continue as per the scheduled visits per Table 7-1 and Table 7-2 until disease recurrence, withdrawal of consent by the subject, subject is lost to follow up, death or the sponsor terminates the study.

A whole body bone scan (e.g. Tc-99m bone scan, sodium fluoride PET [NaF-PET] bone scan) can be done to identify location of recurrence in bone tissue. If bone metastases were identified by a bone scan, it has to be confirmed histologically (preferred) or radiographically (by CT, MRI or FDG-PET-CT) if biopsy confirmation is unsafe.

All MRI and CT should be done with contrast unless contraindicated. If a subject is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (Chest MRI is not recommended due to respiratory artifacts, however if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

Brain MRI with contrast is required. If a subject has known contraindication or develops contraindication to MRI contrast media, MRI without contrast may be acceptable as long as the image quality and the slice thickness (5mm or less is recommended) is high enough to confirm disease-free status, and after discussion and approval by a Novartis study physician.

[redacted]

Findings from radiological evaluations (evaluation of suspicion of recurrence or unconfirmed findings) will be recorded in the eCRF.

Table 7-3 Imaging Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement)	Mandated	Mandated, every 12 weeks for the first year and every 26 weeks for years two and three
Brain MRI	Mandated	If clinically indicated (upon signs or symptoms of CNS metastases)
Whole body bone scan	If clinically indicated	If clinically indicated (new bone pain or other symptoms of bone metastases)
Chest and abdomen (including full liver and bilateral adrenal imaging) low-dose non-contrast CT or MRI (contrast may be added at investigator's discretion)	Not done	Mandated, every 12 months for years four and five
Unscheduled CT or MRI of involved area, upon any signs or symptoms of recurrence	Not applicable	Upon suspected recurrence

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing Eastern Cooperative Oncology Group (ECOG) Performance Status, vital signs, weight, ECG (at select visits), Patient Reported Outcomes, laboratory assessments including hematology, chemistry, coagulation, and urinalysis, as well as collecting adverse events and performing physical exams at every visit. For details on AE collection and reporting, refer to Section 8.

As per Section 2.7 Rationale for public health emergency mitigation procedures during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur for safety monitoring and discussion of the subject´s health status until it is safe for the subject to visit the site again. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures.

7.2.2.1 Determination of tuberculosis status

Determination of tuberculosis status, is required before administration of study drug and must be performed according to the locally approved evaluation methods as per local clinical practice or guidelines. In subjects without active tuberculosis, if the results of the evaluation require treatment, then the treatment should be initiated before randomization (unless otherwise required by Health Authorities or IRB in which case curative treatment must be completed prior to screening). TB In countries with no local tuberculosis guidelines, CDC guidelines may be used (httpswwwcdcgov/tb/default.htm). The QuantiFERON-TB Gold Plus (QFT-Plus) assay, is offered through central lab, as an option.

[redacted]

7.2.2.2 Physical examination

The physical examination comprises a total body examination that should include: general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological review. If indicated, rectal, external genitalia, breast and pelvis exams will be performed. Information about the physical examination must be present in the source documentation at the study site. Physical examination is to be performed according to the visit schedule as outlined in Table 7-1.

Significant findings that were present prior to the signing of informed consent must be included in the medical history eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the adverse event eCRF.

7.2.2.3 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, and body temperature.

7.2.2.4 Height and weight

Height will be measured at screening (without shoes).

Body weight (in indoor clothing, but without shoes) will be measured at screening and at subsequent time points as specified in Table 7-1.

7.2.2.5 Performance status

The performance status will be assessed according to the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale as specified in Table 7-4 (Oken 1982) following the schedule given in Table 7-1.

Table 7-4 ECOG Performance Status

Grade	ECOG status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7.2.2.6 Laboratory evaluations

Central and/or local laboratories (with normal range provided) will be used for the analysis of scheduled hematology, biochemistry, and coagulation specimens collected as part of safety monitoring (as detailed in Table 7-1). Other blood specimens collected as part of safety monitoring (e.g., HIV screen, HBsAg, HCV antibody) will be analyzed by central laboratories. Dipstick urinalysis (macroscopic panel) will be performed at the site (unless local institution policies dictate otherwise), and in the case of any out of range parameters, a urine sample will be sent to central laboratory for further analysis (microscopic panel). Laboratory values

[redacted]

obtained during the Screening phase will be used to assess subject's eligibility. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 7.1).

When using central laboratory analysis, the site does not need to wait for the results of centrally-analyzed laboratory assessments when an immediate clinical decision needs to be made (e.g. confirmation of eligibility, study drug interruption, re-initiation, and/or termination) and locally unscheduled results may be used. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators separately.

Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the Central Laboratory Manual/Flowchart. Visit windows of ± 3 days are allowed for all visits beyond Cycle 1 during the treatment phase.

If at any time a subject has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory. The investigator is responsible for reviewing all laboratory reports for subjects in the study and evaluating any abnormalities for clinical significance.

The results of the local laboratory will be recorded in the eCRF if any the following criteria are met:

- A treatment decision was made based on the local results, or
- There are no concomitant central results available, or
- Local lab results document an AE not reported by the central lab, or
- Local lab results document an AE where the severity is worse than the one reported by the central lab.

At any time during the study up to safety follow-up, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. The severity of laboratory data will be graded using the Common Terminology Criteria for Adverse events (CTCAE) version 5.0. Additional analyses are left to the discretion of the investigator.

Table 7-5 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, Red blood cells (RBC), White blood cells (WBC) with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils in percentage or absolute)
Chemistry	Albumin, ALT, AST, calcium (at screening, calcium corrected for albumin will be tested in addition to calcium), creatinine, creatinine clearance, total bilirubin, direct bilirubin (only if total bilirubin is ≥ grade 2), blood urea nitrogen (BUN) or urea, magnesium, potassium, sodium, fasting glucose, phosphate (inorganic phosphorus), alkaline phosphatase, total serum amylase, pancreatic amylase (as needed), lipase, GGT
hs-CRP*	Biomarker assessment to be performed in Central Laboratory Testing
Urinalysis	Macroscopic panel (Dipstick) (Color, bilirubin, Blood, Glucose, Ketones, Leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells)

[redacted]

Test Category	Test Name
Pregnancy	At screening visit and EOT, serum pregnancy test If local requirements dictate otherwise, local regulations should be followed
Coagulation	Activated Pro-thrombin time (aPTT) and International normalized ratio (INR) or Quick Test
Hepatitis/ Infectious markers	TB, HIV, HbsAg, HCV antibodies. (Japan only: HBc and HBs antibodies)
*For China only: biomarker collection is conditional upon approval from HA, EC and additional authorities (i.e. HGRAC).	

7.2.2.6.1 Hematology

Hematology tests are to be performed according to the visit schedule outlined in Table 7-1. For details of the Hematology panel see Table 7-5.

Hematology should be assessed on the actual scheduled day, even if study drug is being withheld.

7.2.2.6.2 Clinical chemistry

Biochemistry tests are to be performed according to the visit schedule outlined in Table 7-1. For details of the Biochemistry panel see Table 7-5. Biochemistry should be assessed on the actual scheduled day, even if study drug is being withheld. Estimate of GFR (via estimated creatinine clearance rate) will be done centrally using the Cockcroft-Gault formula.

Estimated creatinine clearance rate (eC_{Cr}) using Cockcroft-Gault formula

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

When serum creatinine is measured in µmol/L:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where *Constant* is *1.23* for men and *1.04* for women.

7.2.2.6.3 High-sensitivity C-reactive protein (hs-CRP) and High-sensitivity Interleukin-6 (hs-IL-6)

This marker of inflammation will be monitored according to the visit schedule outlined in Table 7-1 and Table 7-5. Sample handling and shipping instructions will be provided in the Laboratory Manual. Results for hs-CRP and hs-IL-6 will not be communicated to the investigative sites during study conduct and will remain blinded until the time of database lock.

7.2.2.6.4 Coagulation

7.2.2.6.5 INR and aPTT are to be performed according to the visit schedule outlined in Table 7-1. Urinalysis

Urinalysis is to be performed according to the visit schedules outlined in Table 7-1. For details of the urinalysis panel see Table 7-5.

[redacted]

7.2.2.6.6 Pregnancy and assessments of fertility

During screening, a serum pregnancy test will be completed (Day -28 to Day -1). On Cycle 1 Day 1 prior to dosing and at subsequent cycles, a urinary pregnancy test (dipstick) will be performed. A serum pregnancy test will also be completed at EOT. The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit. Refer to Table 7-1. If local requirements dictate otherwise, local regulations should be followed.

As per Section 2.7, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant subjects can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the subject so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Women who are determined not to be of child bearing potential before the study will only be tested at screening. When non-child bearing potential status is determined during the study, further pregnancy testing will not be continued. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), and otherwise not of child bearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks prior to first dose of study drug. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential (such testing is not covered as part of the study assessments). If local requirements dictate otherwise, local regulations should be followed.

If a positive pregnancy test is performed in between study visits, the subject must immediately notify the investigator.

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

Local single 12-lead ECGs should be recorded after the subject has been resting for 5-10 min prior to the timepoint indicated in Table 7-1.

An unscheduled ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Interpretation of the tracing must be made by a qualified physician and documented in the appropriate eCRF.

Each ECG tracing should be labeled with the study number, subject initials (where regulations permit), subject number, date, and kept in the source documents at the study site. Clinically significant ECG abnormalities present at screening should be reported on the appropriate eCRF. New or worsened clinically significant findings occurring after informed consent must be recorded on the appropriate eCRF.

[redacted]

7.2.3 Pharmacokinetics, immunogenicity and pharmacodynamics

7.2.3.1 Pharmacokinetic, immunogenicity and pharmacodynamics blood collection and handling

Time points of blood sample collection for canakinumab PK, IG and PD are outlined in Table 7-6. If a subject starts new antineoplastic therapy after discontinuing study treatment, no further PK/PD/IG samples need to be collected. Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

For each scheduled PK sample, 2.5 mL of blood will be collected into SST tubes. The blood sample will be allowed to clot over a minimum of 30 minutes at room temperature prior to harvesting of the serum. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. Serum PK samples will be split into 2 aliquots of approximately 0.5 mL serum (polypropylene tubes) and then stored (within 30 min of preparation) at -24˚C (approximately) prior to shipment to the Sponsor or central lab (see sample storage information below for detailed stability information). One aliquot will be shipped on dry ice to the analytical laboratory. The remaining aliquot must be kept at the central lab as a backup sample. Remaining samples will only be disposed of after approval by Novartis.

For each scheduled IG sample, 2.5 mL of blood will be collected into SST tubes. The blood sample will be allowed to clot over a minimum of 30 minutes at room temperature prior to harvesting of the serum. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. Serum IG samples will be split into 3 aliquots of approximately 0.3 mL serum (polypropylene tubes) and then stored (within 30 min of preparation) at -70˚C (approximately) prior to shipment to the Sponsor or central lab (see sample storage information below for detailed stability information). Two aliquots will be shipped on dry ice to the analytical laboratory. The remaining aliquot must be kept at the central lab as a backup sample. Remaining samples will only be disposed of after approval by Novartis. If anaphylactoid reactions occur after injection, two more samples (at the time of the event and 8 weeks later) need to be taken.

For each scheduled PD (IL-1β) sample, 3.5 mL of blood will be drawn into SST tubes, to obtain 1.5 mL serum. The sample will be allowed to clot during 45 minutes at room temperature. The serum will be obtained by centrifugation at approximately 2500 g for 10 minutes. The sample will be split into two aliquots of 0.7 mL to be transferred into freezer-proof polypropylene screw-cap tubes. Serum tubes will be frozen within 90 min of venipuncture and kept at -24°C pending shipment on dry ice. One aliquot will be shipped on dry ice to the analytical laboratory. The remaining aliquot must be kept at the central lab as a backup sample.

On days and time points where blood IG and PD samples are to be drawn, the PK sample must be drawn first. The exact collection date and time of all samples must be documented on the PK, IG and PD blood collection eCRF pages. The date and exact time of dosing, as well as the date and actual time of blood sampling must be recorded on the eCRF.

All samples will be given a unique sample number and a dose reference ID.

Further details on labeling of the PK, IG and PD samples, instructions for the collection, handling and shipment of samples can be found in the [CACZ885T2301 laboratory manual]. If subjects experience a SAE or an AE leading to the discontinuation of the study treatment, an unscheduled PK and IG blood sample should be obtained as close as possible to the event

[redacted]

occurrence. The date and time of the last dose and the time of PK and IG blood draw should be recorded.

[redacted] Collection of PK, PD and/or IG samples may be stopped upon decision of the Sponsor, if/when sufficient data are collected, after the primary CSR cut-off date is reached or following decision to stop the study.

Table 7-6 Blood collection (serum) for canakinumab pharmacokinetics (PK), immunogenicity (IG) and pharmacodynamics (PD)

Dose Reference Identification (ID)		PK sample number	IG sample number[b]	Total IL-1β (PD) sample number[b]	Scheduled time points (hours)			
Dose ID following sampling	Dose ID prior to sampling*				Cycle	Day	Scheduled time (hours)	Description
1	-	101	201	301	1	1	0 hr[a]	Pre-dose
-	-	104	-	-	1	8	168 hr (±12h)	Post-dose
1	-	105	-	302	1	15	336 hr (±24h)	Post-dose
2	1	106	202	-	2	1	0 hr (or 504 hr post-C1D1 dose)	Pre-dose
3	400	107	203	303	4	1	0 hr	Pre-dose
4	401	108	204	-	6	1	0 hr	Pre-dose
5	402	111	205	-	9	1	0 hr	Pre-dose
6	403	112	206	304	12	1	0 hr	Pre-dose
-	-	115	209	306	18/EOT**	NA	Anytime	Pre/Post-dose**
-	-	116	210	307	safety follow-up 1	NA	Anytime	-
-	-	117	-	-	safety follow-up 2	NA	Anytime	-
-	-	118	211	308	safety follow-up 3	NA	Anytime	-
-	-	119	-	-	safety follow-up 4	NA	Anytime	-
-	-	120	212	309	safety follow-up 5	NA	Anytime	-
NA	NA	1001+[c]	2001+[d]	3001+[e]	NA	NA	Unscheduled and at the time of progression or AE	-

[redacted]

Dose Reference Identification (ID)		PK sample number	IG sample number[b]	Total IL-1β (PD) sample number[b]	Scheduled time points (hours)			
Dose ID following sampling	Dose ID prior to sampling*				Cycle	Day	Scheduled time (hours)	Description
* These dose reference IDs refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK, IG and PD sample.								
** This collection is mandatory for all subjects that end or complete study treatment. If the subject completes treatment, this sample will be collected pre dose for cycle 18. If the subject presents for EOT visit as a result of discontinuation, then this will be a post-dose collection relative to the last dose administered.								
[a] Sample should be taken immediately prior to the next administration of canakinumab.								
[b] IG and PD samples are to be collected together with PK samples at the same time.								
[c] PK sample numbers for any unscheduled PK collection will start with 1001.								
[d] IG sample numbers for any unscheduled IG collection will start with 2001.								
[e] PD sample numbers for any unscheduled PD collection will start with 3001.								

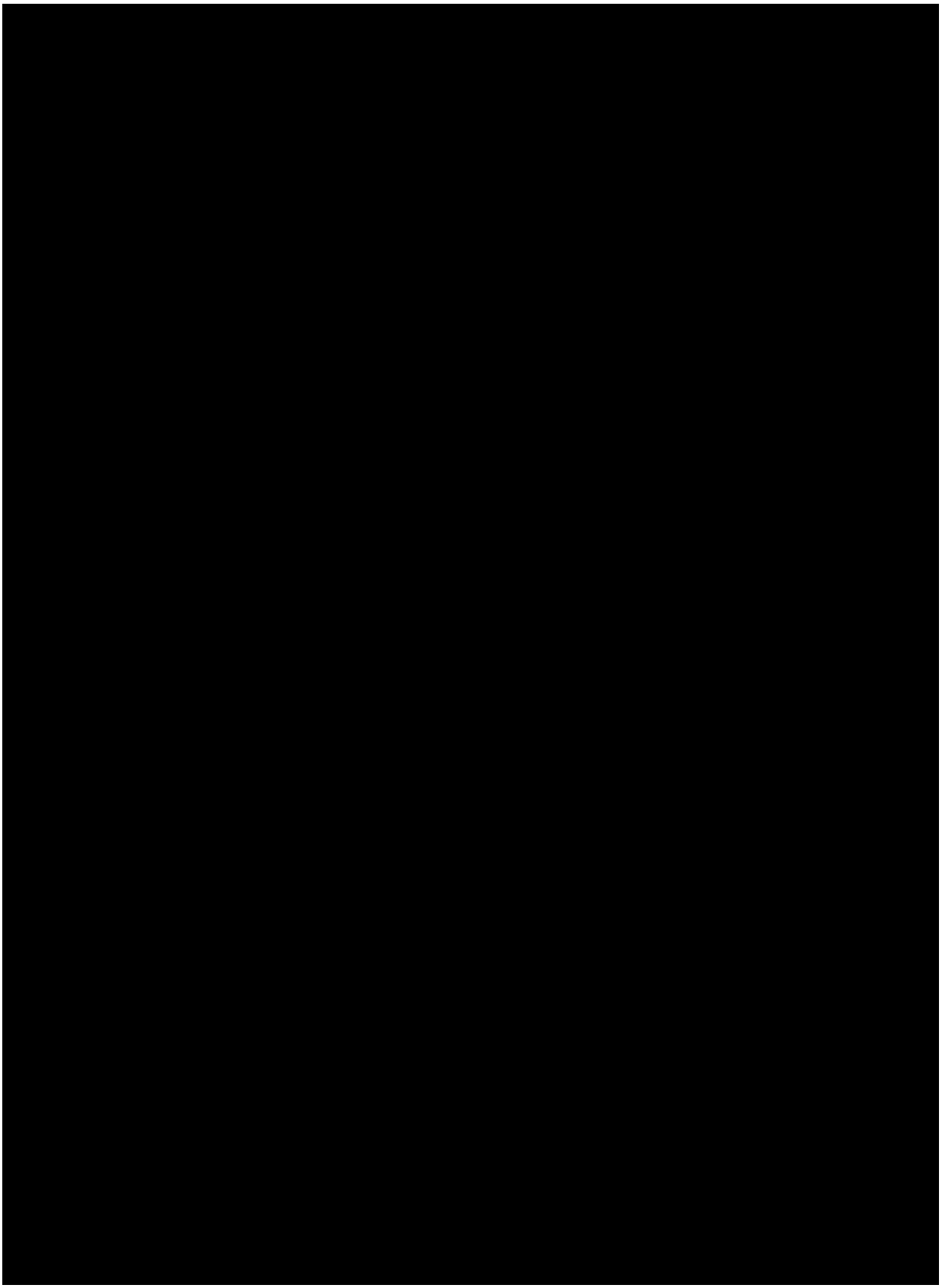
7.2.3.2 Analytical method

An ELISA method will be used for bioanalytical analysis of ACZ885 in serum, with an anticipated lower limit of quantification (LLOQ) of 100 ng/mL for samples analyzed in China and 300 ng/mL for all other samples. The detailed method description to assess ACZ885 concentration will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR).

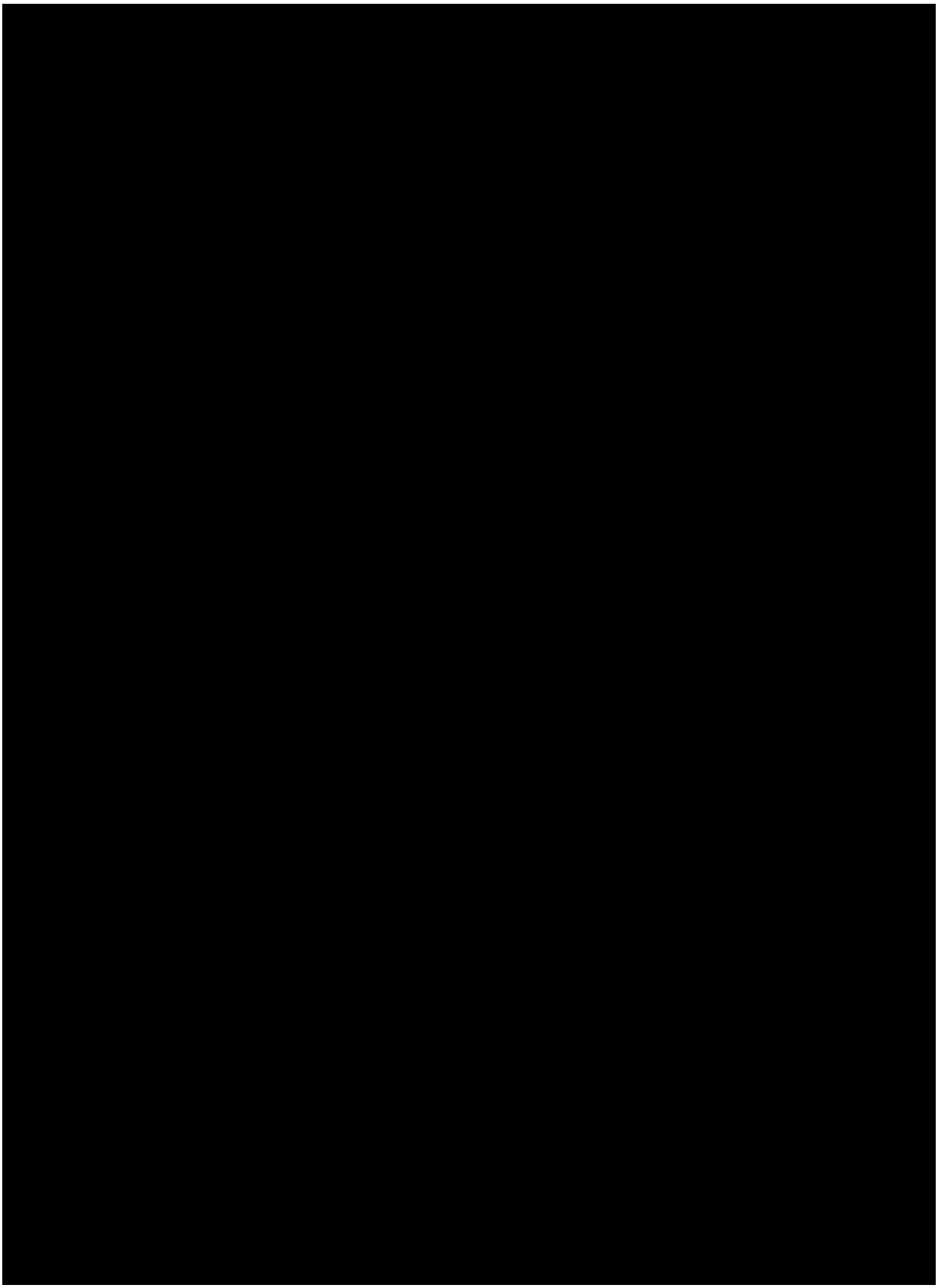
A Meso Scale Discovery (MSD) electrochemiluminescence assay based method will be used for the detection of potential anti-ACZ885 antibody formation. The detailed method description to assess immunogenicity will be described in the bioanalytical raw data of the study and in the respective BDR.

An ELISA method will be used for bioanalytical analysis of total IL-1β in serum, with an anticipated LLOQ of 0.299 ng/mL. The detailed method description to assess PD concentration will be described in the bioanalytical raw data of the study and in the respective BDR.

[redacted]



[redacted]



[redacted]

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[redacted]

7.2.4.2 Biomarker sample collection sub-study (CACZ885T2301A) in non-small cell lung cancer subjects that are candidates for curative surgery*

NSCLC subjects who are candidates for complete resection surgery (and therefore, prospective candidates for the main study, CACZ885T2301) will be asked to participate in a biomarker sub-study (CACZ885T2301A). In this sub-study, pre- and post-surgery blood samples will be collected to evaluate biomarkers involved in the IL-1β inflammatory pathway as well as mutations present in blood prior to surgery (see Table 7-2).

The sub-study will be identified as CACZ885T2301A. Signature of a separate informed consent form will be required before any samples are collected. Lack of participation in the sub-study does not exclude subject's ability to participate in the main study, CACZ885T2301.

Enrollment into the sub-study will end when the enrollment into the main study has been completed.

The scope of this sub-study is limited to the collection of samples as described in Table 7-2.

Data for this sub-study will be collected in a separate database with unique subject IDs (Refer to Section 6.5.1).

*For China only: biomarker collection is conditional upon approval from HA, EC and additional authorities (i.e. HGRAC).

7.2.5 Other assessments

7.2.5.1 Anti-ACZ885 antibodies (immunogenicity assessment)

To assess potential immunogenicity, serum samples for determination of anti-canakinumab antibodies will be collected during the study according to the visit schedule outlined in Table 7-1.

7.2.6 Patient reported outcomes

7.2.6.1 PRO Questionnaires

The European Organization for Research and Treatment of Cancer's core quality of life questionnaire EORTC-QLQC30 (version 3.0) and it's lung cancer specific module QLQ-LC13 (version 1.0) will be used to collect data on the subject's functioning, disease-related symptoms, health-related quality of life, and health status. The EQ-5D-5L will be used for the purpose of the computation of utilities that can be used in health economic studies. The EORTC QLQ-C30/LC13 as well as the EQ-5D-5L are reliable and valid measures frequently used in clinical

[redacted]

trials of subjects with lung cancer and previously used in the adjuvant setting (Bezjak et al 2008).

The EORTC-QLQC30 is a self-reporting 30-item generic instrument for use in cancer subjects across tumor types including lung cancer. It assesses 15 domains consisting of 5 functional domains (physical, role, emotional, cognitive, social) and 9 symptom domains (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) and a global health status or HRQoL scale (Aaronson et al 1993).The EORTC QLQ-LC13 complements the QLQ-C30, and measures disease symptoms and treatment-related adverse effects. The lung cancer module incorporates one multi-item scale to assess dyspnea, and 9 single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis (Bergman et al 1994).

All of the domain scores of the EORTC-QLQC30 and QLQ-LC13 range from 0 to 100. A high score indicates a higher response level. Hence, a high score for a functional scale indicates a high and healthy level of functioning but a high score for a symptom scale indicates a high level of symptoms/problems.

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990). The EQ-5D-5L is designed for self-completion by respondents and takes only a few minutes to complete. Instructions to respondents are included in the questionnaire. The EQ-5D-5L consists of 2 pages – the descriptive system and the EQ visual analogue scale (EQ VAS) (Herdman M et al 2011). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'.

[redacted]

7.2.6.2 PRO assessments

PRO questionnaires (EORTC QLQ-C30/LC13 and EQ-5D-5L) will be provided at the visits indicated in Table 7-1, i.e. at screening, after randomization every 3 weeks for 18 cycles, at EOT, every 4 weeks during the 130-day safety follow up, every visit before any radiological assessment is done for recurrence, before any unscheduled imaging assessments and two follow up visits after documented disease recurrence (one within 7 days and one within 28 days after discussing disease recurrence with the subject).

All questionnaires should be provided in the subject's local language at the beginning of the study visit prior to any interaction with the study investigator including any tests, treatments or receipt of results from any tests to avoid biasing the subject's perspective. This is to avoid potentially biasing subjects or their responses to study questionnaires.

PRO data will be recorded by subjects onto an electronic tablet device maintained at the study site. Investigators or study personnel should provide technical assistance but should not encourage the subjects to change responses reported in questionnaires.

Subjects should be given sufficient space and time to complete all study questionnaires. Subjects should be encouraged to complete any missing responses. Attempts should be made to collect responses to all questionnaires for all subjects, including from those who discontinue prior to the study evaluation completion visit, however, if subjects refuse to complete questionnaires, this should be documented in study source records. Subjects' refusal to complete study questionnaires are not protocol deviations.

Questionnaires should be completed before any other clinical assessments planned for the study visit.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after a subject's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the AE eCRF. Conditions that were already present at the time of informed consent should be recorded in the medical history eCRF. Adverse event monitoring should be continued for at least 130 days following the EOT visit. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

[redacted]

If a new antineoplastic therapy is initiated after discontinuation of study treatment, only SAEs suspected to be related to study treatment will be collected in the Adverse Events eCRF.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an adverse event or not) will also be collected though a death form.

The occurrence of adverse events should be sought by non-directive questioning of the subject during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- The severity grade (CTCAE v5.0 Grades 1-5)
- Its duration (Start and end dates)
- Its relationship to the study treatment. Reasonable possibility that AE is related:
  - No (i.e. not treatment-related);
  - Yes, investigational treatment (i.e. related to treatment with canakinumab/placebo);
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Whether it is serious, where an SAE is defined as in Section 8.2.1 and which seriousness criteria have been met
- Outcome (not recovered/not resolved, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the AE eCRF.

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 treatment, the interventions required to treat it, and the outcome.

[redacted]

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the AE eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for adverse events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an adverse event should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data and include:

- infections/opportunistic infections,
- neutropenia,
- abnormal liver parameters,
- thrombocytopenia,
- immunogenicity/allergenicity,
- autoimmunity reactions,
- new primary malignancy,
- interactions with vaccines,
- interactions with drugs eliminated by CYP450 enzymes,
- pulmonary complications (pulmonary hypertension and interstitial lung disease)
- injection site reactions.

Details regarding these adverse events are provided in the [canakinumab Investigator's Brochure]. Potential emergent new AEs will be monitored during the course of the study.

Canakinumab is associated with an increased incidence of serious infections during and after treatment. Therefore subjects should be carefully monitored for signs and symptoms of

[redacted]

infections during and after treatment with canakinumab. Physicians should exercise caution when administering canakinumab to subjects with infections, a history of recurring infections, or underlying conditions which may predispose them to infection.

Neutropenia has been observed with medicinal products that inhibit IL-1β, including canakinumab.Treatment should not be initiated in subjects with neutropenia. It is recommended that neutrophil counts be assessed before and during treatment.

8.2 Serious adverse events

8.2.1 Definitions

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- Is fatal
- Life-threatening

Note: Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect, fetal death or a congenital abnormality or birth defect
- Requires in subject hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the subject's general condition
    - 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
- Is medically significant, i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

[redacted]

Confirmed COVID-19 infection should be considered as medically significant and should therefore be reported as an SAE.

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

8.2.2 SAE Reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until at least 130 days after the subject has stopped study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. In case of technical issue to report SAE information via eSAE, the site must complete paper SAE form to meet 24-hour reporting timeline; once the issue is resolved, the site must enter the SAE information in eSAE database.

If a new antineoplastic therapy is initiated after discontinuation of study treatment, only SAEs suspected to be related to study treatment will be collected in the Adverse Events eCRF.

For SAE reporting in case of malignancies during the study, the following applies:

- Recurrence of NSCLC malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event, except if the investigator considers that progression of malignancy is related to study treatment. Adverse events separate from the recurrence of NSCLC malignancy (example, deep vein thrombosis at the time of recurrence or hemoptysis concurrent with finding of disease recurrence) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.
- New primary lung cancer malignancies should always be reported as SAEs.
- New primary malignancies in organs other than lung should always be reported as SAEs.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

[redacted]

Any SAEs experienced after the 130-day safety follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

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

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. 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 subject 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 treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Applicable for sub-study:

Only SAEs related to the blood sample collection in the sub-study will be collected.

8.3 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential for effective treatment of the subject. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Unblinding is also permitted under exceptional circumstances if treatment assignment is critical to determine the optional subsequent treatment for the subject and only if post-progression therapy with an IL-1β inhibitor is being considered. In case of unblinding for determination of subsequent treatment, approval by a Novartis study physician is required. Emergency code breaks are performed using the IRT. When the investigator contacts the IRT to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. The investigator will then receive details of the drug treatment for the specified subject and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Lead that the code has been broken.

[redacted]

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- Protocol number
- Subject number

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

Study treatment must be discontinued once emergency unblinding has occurred. The subject will have an EOT visit completed and will continue to be followed for recurrence as specified in the protocol. Subject will remain in follow-up unless withdrawn from study.

8.4 Pregnancies

If a female subject becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial subject. The subject must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure subject safety, each pregnancy occurring while the subject is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form. If a subject becomes pregnant while on study treatment, the newborn will be followed for up to 12 months.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided [canakinumab Investigator Brochure]. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

8.6 Data Monitoring Committee

This study will institute a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be constituted prior to the randomization of the first subject. The DMC will be responsible to review safety data approximately 6 months

[redacted]

for the first 18 months after the first randomized subject has started study treatment (first meeting will be conducted when approximately 50 subjects have been treated) and approximately every 1 year thereafter until all subjects have completed 18 cycles (approximately 54 weeks) of treatment or final DFS analysis (whichever occurs earlier). The DMC will also be responsible to review efficacy and safety data in the conduct of the interim DFS analyses as defined in the protocol. This includes but does not limit the role of the DMC to evaluate these data and to provide recommendations to the sponsor to continue, modify or stop the study early.

It is expected that the DMC will consist at a minimum of two physicians with appropriate disease area qualifications and one statistician. There will be a meeting with the DMC describing their roles and responsibilities and discussing potential data format and process issues prior to the finalization of DMC charter and the interim analysis plan.

8.7 Steering Committee

The steering committee will be established comprising investigators participating in the trial, i.e. not being members of the DMC or Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

[redacted]

9.2 Site monitoring

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

The investigator must maintain source documents for each subject 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 recorded on eCRFs must be traceable to source documents in the subject's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into the eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Blood, plasma/serum and tumor samples for laboratory data and biomarkers assessments will be collected by sites and sent to the Novartis designated central laboratory for processing. The laboratory results and IRT data will be sent electronically to Novartis. PRO data will be recorded by subjects onto an electronic tablet device maintained at the study site. The device will be programmed to ensure that all relevant observations are recorded.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

[redacted]

Concomitant treatments and prior 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.

Samples and/or data (e.g. biomarkers, safety samples) will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO). PRO data collected using an electronic tablet device will be documented into a separate study-specific database supplied and managed by a designated vendor. The PRO database will be accessible to study sites and Novartis personnel (or a designated CRO) for data management. All PRO data will be sent electronically to Novartis personnel (or a designated CRO).

Randomization codes and data about all study treatments dispensed to the subject and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

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 personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the treatment codes will be unblinded and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator/ designee will generate Patient Data Report from EDC and archive at the investigational site.

10 Statistical methods and data analysis

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises of all subjects to whom study treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment and strata (AJCC/UICC v. 8 stage: IIA versus IIB versus IIIA versus IIIB with T>5cm N2 disease; Histology: squamous versus non-squamous; and Region: Western Europe and North America vs. eastern Asia vs. Rest of the world (RoW)) to which they have been assigned during the randomization procedure.

10.1.2 Safety set

The Safety Set includes all subjects who received at least one dose of study drug. Subjects will be analyzed according to the study treatment they received, either canakinumab or placebo. The treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

[redacted]

10.1.3 Dose-determining analysis set

Not applicable

10.1.4 Pharmacokinetic analysis set

The Pharmacokinetic Analysis Set (PAS) consists of all subjects who received at least one dose of study drug and have at least one evaluable pharmacokinetic (PK) sample. The definition of an evaluable PK blood sample will be further specified in the SAP.

10.1.5 Other analysis sets

Other analysis sets, if needed, will be specified in the SAP.

10.2 Subject demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment arm for the FAS. In light of COVID-19 pandemic impacting the study during the enrollment phase, it will be summarized by pandemic phases: pre-pandemic period and pandemic period.

Participant race and ethnicity are collected to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics (mean, standard deviation, median, minimum, and maximum) will be presented.

Relevant medical histories and current medical condition at baseline will be summarized by system organ class , preferred term, and treatment arm.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, summary statistics (mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum) will be presented.

The duration of exposure to canakinumab and placebo, as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized by treatment arm by means of descriptive statistics using the safety set.

The number of subjects with dose adjustments (interruption, or permanent discontinuation) and the reasons will be summarized by treatment arm. All dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment arm.

[redacted]

10.4 Primary objective

The primary objective is to compare the DFS in the canakinumab versus placebo arms as determined by local investigator assessment.

10.4.1 Variable

The primary efficacy variable of the study is DFS, defined as the time from the date of randomization to the date of the first documented NSCLC disease recurrence as assessed by local investigator radiologically or death due to any cause. Disease recurrence includes diagnoses of new primary lung malignancies. Clinical deterioration is not considered as a recurrence of disease. In case of non-conclusive radiological evidence, a biopsy assessment will be performed to confirm NSCLC recurrence; radiological assessment date will be used as DFS event date. DFS events will be assessed locally. Censoring conventions are provided below in Section 10.4.3.

10.4.2 Statistical hypothesis, model, and method of analysis

Assuming proportional hazards model for DFS, the following statistical hypotheses will be tested to address the primary efficacy objective:

H_{01} (null hypotheses): $\Theta_1 \geq 0$ vs. H_{a1} (alternative hypotheses): $\Theta_1 < 0$

Where Θ_1 is the log hazard ratio of DFS in the canakinumab (investigational) arm vs. placebo (control) arm.

The primary efficacy analysis to test this hypothesis and compare the two treatment groups will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance. The stratification will be based on the following randomization stratification factors: AJCC/UICC v. 8 stage IIA versus IIB versus IIIA versus IIIB with T>5cm N2 disease; Histology: squamous versus non-squamous; and Region: Western Europe and North America vs. eastern Asia vs. Rest of the world (RoW). The primary efficacy variable, DFS, will be analyzed at one interim analysis enabling the study to stop due to futility and final analysis of a group sequential design, using a Lan-DeMets (O'Brien-Fleming) α-spending function and a non-binding user-defined β-spending function (gamma function with γ=-3). Analyses will be based on the FAS population according to the treatment group and strata assigned at randomization. The DFS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves will be presented for each treatment group. The DFS Kaplan- Meier estimate along with 95% confidence intervals will be presented at different time points (e.g. 1 year, 2 years, 3 years, 4 years, 5 years) for each of the two treatment arms. The hazard ratio for DFS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test.

10.4.3 Handling of missing values/censoring/discontinuations

DFS will be censored if no DFS event is observed prior to the analysis cut-off date or subjects who received any subsequent anti-neoplastic therapy for NSCLC. The censoring date will be the date of last assessment before the cut-off date or NSCLC related anti-neoplastic therapy date.

[redacted]

10.4.4 Supportive and Sensitivity analyses

As sensitivity analyses performed in the FAS, the hazard ratio and 95% confidence interval for DFS will be obtained from:

- an unstratified and covariate unadjusted Cox model.
- stratified Cox model using a modified definition of DFS event with the inclusion of the start of anti-neoplastic therapy as a DFS event in addition to NSCLC disease recurrence defined for primary analysis.
- stratified Cox model without censoring NSCLC related anti-neoplastic therapy
- stratified Cox model with censoring two or more missing assessments
- stratified Cox model with censoring subjects when discontinuing treatment or death due to COVID-19, or receiving COVID-19 medications
- a stratified and covariate adjusted Cox model including covariates such as gender, age and smoking history.

The final list of covariates to be included in the model will be provided in the SAP.

If the primary analysis is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed including AJCC/UICC v.8 stage, histology and region. Other subgroups to be considered will be defined in the SAP.

The number of subjects censored and reasons for censoring for DFS will be summarized by treatment group using descriptive statistics.

10.5 Secondary objectives

Secondary objectives of the study are as specified in Table 3-1. The secondary objectives in this study are to compare the two treatment groups with respect to overall survival (OS), lung cancer specific survival (LCSS), DFS and OS in PD-L1 and CD8 subgroups, time to 10 point definitive deterioration and first 10 point definitive deterioration in patient-reported outcomes, including key symptom scores, and safety. OS is identified as the key secondary endpoint. A hierarchical testing strategy will be used to control the overall type I error rate, where OS will only be formally tested and interpreted if the primary analysis of DFS is statistically significant.

10.5.1 Key secondary objective(s)

The key secondary objective is to determine whether treatment with canakinumab prolongs OS compared with placebo arm. OS is defined as the time from the date of randomization to the date of death due to any cause. If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cut-off date).

Assuming proportional hazards model for OS, the following statistical hypotheses will be tested only if DFS is statistically significant:

H_{02} (null hypotheses): $\Theta_2 \geq 0$ vs. H_{a2} (alternative hypotheses): $\Theta_2 < 0$

Where Θ_2 is the log hazard ratio of OS in the canakinumab (investigational) arm vs. placebo (control) arm. The analysis to test these hypotheses will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance. The stratification will be based on the following

[redacted]

randomization stratification factors: AJCC/UICC v. 8 stage IIA versus IIB versus IIIA versus IIIB T>5cm N2 disease; Histology: squamous versus non-squamous; and Region: Western Europe and North America vs. eastern Asia vs. Rest of the world (RoW).

OS analyses will be conducted as part of a group sequential design using a Lan-DeMets (O'Brien-Fleming) α spending function (a separate function to that used for DFS). Analyses will be based on the FAS population according to the randomized treatment group and strata assigned at randomization. The OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

OS will be tested hierarchically:

- If DFS is statistically significant at the final analysis, OS will be tested. If OS is not
- statistically significant at this stage, an additional IA for OS and a final OS analysis will be planned at approximately 418 deaths and 504 deaths respectively.
- If DFS is not statistically significant at the final analysis for DFS, OS will not be tested.

The number of subjects censored and reasons for censoring for OS will be summarized by treatment group using descriptive statistics.

10.5.2 Other secondary efficacy objectives

In order to evaluate the effect of canakinumab within PD-L1 subgroups, DFS and OS analyses will be performed by PD-L1 subgroups with 1% cut-off on tumor cells (TC) to define positive or negative status as determined by IHC. Additionally, PD-L1 subgroups will also be assessed using ≥ 50% cut-off. Therefore, a comparison between <1%, ≥1-49%, and ≥ 50% PD-L1 expression level subgroups will be done.

In order to evaluate the effect of canakinumab within CD8 subgroups, DFS and OS analyses will be performed by CD8 subgroups with the median and quartiles (including quartile-complements, e.g. below lower quartile and above lower quartile) of baseline CD8 as cut-offs. In addition, the relation between CD8 expression in resected tumor sample and clinical outcome will be evaluated using CD8 as continuous, potentially log-transformed, co-variate as well as categorical covariates in a Cox model. These analyses will support the establishment of CD8 as a prognostic/predictive factor if there is an expressions level correlating to clinical outcome.

Lung cancer specific survival (LCSS) is defined as the time from the date of randomization to the date of death due to lung cancer. Analyses will be based on the FAS population according to the randomized treatment group and strata assigned at randomization. The LCSS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for LCSS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

[redacted]

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment arm.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of subject's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study treatment to 130 days after last dose of study treatment
3. post-treatment period: starting at day 131 after last dose of study treatment.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs with onset date during the on-treatment period, the treatment-emergent AEs.

The incidence of treatment-emergent adverse events will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, and relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated. AESIs will be defined based on the current case retrieval strategy (CRS).

All reported deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those starting during the pre-treatment and post-treatment period will be flagged.

10.5.3.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

For laboratory tests where grades are not defined by CTCAE 5.0, results will be categorized as low/normal/high based on laboratory normal ranges. If required, for certain laboratory parameter, values lower than lower limit of normal (LLN) or higher than upper limit of normal (ULN) may further be summarized into categories based on multiples of LLN or ULN respectively.

The following listings/summaries will be generated separately for hematology, and biochemistry tests:

[redacted]

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v5.0 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v5.0

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v5.0

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

In addition to the above mentioned tables and listings, other analyses if needed, for example figures plotting time course of raw or change in laboratory tests over time or box plots may be specified in the analysis plan.

10.5.3.4 Other safety data

ECG

Notable ECG data will be summarized by treatment. In addition, a listing of these subjects will be produced by treatment arm with notable values flagged.

Vital signs

Notable vital signs will be summarized by treatment. In addition, a listing of these subjects will be produced by treatment arm with notable values flagged.

10.5.3.5 Supportive analyses for secondary objectives

If the primary analysis on OS is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed. The subgroups to be considered will be defined in the SAP.

10.5.3.6 Tolerability

Not applicable

10.5.4 Pharmacokinetics, [redacted] and immunogenicity

PAS will be used in the pharmacokinetic data analysis. Descriptive statistics (n, m (number of non-zero concentrations), mean, CV%, SD, median, geometric mean, geometric CV%, minimum and maximum) for canakinumab concentrations will be presented at each scheduled timepoint. For canakinumab, pre-dose concentrations collected before dose administration on Day 1 of Cycle 2 and beyond are Ctrough.

All concentration data for canakinumab vs. time profiles will be displayed graphically.

[redacted]

10.5.4.1 Data handling principles

Missing values for any PK parameters or concentrations will not be imputed and will be treated as missing.

Below the limit of quantitation (BLQ) values will be set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. BLQ values will be treated as missing for the calculation of the geometric means and geometric CV%.

10.5.4.2 Population pharmacokinetic analysis

If there is adequate amount of data, a mixed-effects model may be applied to the serum canakinumab concentration-time data from this study along with other studies to generate post-hoc estimates of pharmacokinetic parameters using NONMEM to characterize canakinumab exposure and to determine the effects of intrinsic (i.e. demographic factors) and extrinsic covariates (e.g. concomitant medications) on canakinumab exposure. If there is sufficient data for analysis, the details of the population pharmacokinetic analyses may be provided in a separate reporting and analysis plan, and the results may be reported in a separate population pharmacokinetic report.

10.5.4.3 Immunogenicity

Immunogenicity will be characterized descriptively by tabulating anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment.

[redacted]

10.5.5 Resource utilization

Not applicable

10.5.6 Patient-reported outcomes

Three patient-reported outcomes (PRO) questionnaires will be assessed: EORTC QLQ-C30 with QLQ-LC13 incorporated and the EQ-5D-5L. QLQ-C30 and QLQ-LC13 will be considered as the primary scale. Scoring of PRO data and methods for handling of missing items or missing assessments will be handled according to the scoring manual and user guide for each respective subject questionnaire (Fayers 2001, Van Reenen 2015). No imputation procedures will be applied for missing items or missing assessments.

[redacted]

The FAS will be used for analyzing PRO data. Time to definitive 10 point deterioration symptom scores of pain, cough and dyspnea per QLQ-LC13 questionnaire are primary PRO variables of interest. Time to first 10 point deterioration symptom scores of pain, cough and dyspnea per QLQ-LC13 questionnaire, time to first 10 point deterioration of global health status/QoL, shortness of breath and pain per QLQ-C30 questionnaire, time to 10 point definitive deterioration of global health status/QoL, shortness of breath and pain per QLQ-C30 together with the utilities derived from EQ-5D-5L are secondary PRO variables of interest.

Time to deterioration in symptoms and in global health status/QoL are defined as follows:

- The time to definitive 10 point deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10 points absolute increase from baseline (worsening) of the corresponding scale score, with no later change below this threshold i.e. < 10 points was observed or if this increase was observed at the last assessment for the subject, or death due to any cause, whichever occurs earlier. If a subject has not had an event, time to definitive deterioration will be censored at the date of the last adequate assessment. The distribution will be presented descriptively using Kaplan-Meier curves. Summary statistics from Kaplan-Meier distributions will be determined, including the median time to definitive 10 point deterioration along with two-sided 95% confidence interval. Additionally, time to definitive deterioration with different definition for deterioration may be specified in the SAP as deemed appropriate. A stratified Cox regression will be used to estimate the hazard ratio (HR), along with two-sided 95% confidence interval.
- Thetime to first 10 point deterioration is defined as the time from the date of randomization to the first onset of at least 10 points absolute increase from baseline (worsening) in symptoms scores or at least 10 points absolute decrease from baseline (worsening) in global health status/QoL, or death due to any cause, whichever occurs earlier. If a subject has not had an event, time to deterioration will be censored at the date of the last adequate assessment. The distribution will be presented descriptively using Kaplan-Meier curves. Summary statistics from Kaplan-Meier distributions will be determined, including the median time to 10 point deterioration along with two-sided 95% confidence interval. Additionally, time to first deterioration with different definitions for deterioration may be specified in the SAP as deemed appropriate. A stratified Cox regression will be used to estimate the hazard ratio (HR), along with two-sided 95% confidence interval.

Descriptive statistics will be used to summarize the original scores, as well as change from baseline, of the QLQC30/ QLQ-LC13 and EQ-5D-5L at each scheduled assessment time point for each treatment group. Additionally, change from baseline in the scale and subscale values at the time of each assessment will be summarized. Subjects with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

The number of subjects completing each questionnaire and the number of missing or incomplete assessments will be summarized by treatment group for each scheduled assessment time point. No formal statistical tests will be performed for PRO data and hence no multiplicity adjustment will be applied. The FAS will be used for analyzing PRO data.

[redacted]

In addition, a repeated measurement analysis model will be used to compare the treatment groups with respect to changes in all domain scores of the EORTC QLQ-C30/QLQ-LC13 as well as the thermometer and utility scores of the EQ-5D-5L, longitudinally over time. The differences in least square means between the treatment arms and corresponding 95% confidence interval at selected time points will be presented. Details, including handling of missing data, will be specified in the SAP.

[redacted]

[redacted]

[redacted]

10.7 Interim analysis

10.7.1 Disease free survival (DFS)

One interim analysis is planned after approximately 196 of the approximately 392 targeted DFS events (i.e., at approximately 50% information fraction) have been documented. The primary intent of the interim analysis is to stop early for lack of efficacy (futility). There is no intent to carry out an analysis to declare superior efficacy at the time of the interim analysis. An α-spending function according to a two-look (Lan-DeMets) group sequential design with (O'Brien-Fleming) type stopping boundary (as implemented in East 6.4) will be used to construct the efficacy stopping boundaries (Lan and DeMets 1983). A user-defined gamma function with γ=-3 stopping boundary as implemented in East 6.4 will be used as a β-spending function to determine the non-binding futility boundary. The choice of non-binding nature of the futility stopping boundary ensures that the efficacy stopping boundaries are not affected. Based on the choice of α-spending and β-spending function described above and if the interim analysis is performed exactly at 196 DFS events, the futility boundary expressed on the p-value

scale (or the Z-statistic scale) at the first interim is calculated as p = 0.411 (or Z = 0.226). The observed (i.e., nominal) p-value has to be greater than p-value scale futility boundary = 0.411 (or the observed Z-statistic has to be < Z-statistic scale boundary = 0.226) to conclude futility. Since the observed number of events at the interim analysis may not be exactly equal to the planned 196 DFS events, the futility boundary will need to be recalculated using the pre-specified α and β-spending functions and based on the actual number of observed events at interim and the total number of targeted events to calculate the exact information fraction. The observed p-value (or Z-test statistic) at the interim analyses will then be compared against the re-calculated futility boundary.

If the study continues to the final DFS analysis, the final DFS analysis will be performed when approximately 392 DFS events have been documented. If exactly 196 events are observed at the interim analysis, the study continued and exactly 392 events are obtained at the final analysis, the observed p-value will have to be less than 0.024 (or the observed Z statistics has to be > 1.969) to declare statistical significance. In practice, the final analysis will be based on the actual number of DFS events documented at the cut-off date for the final DFS analysis and α already spent at the interim analysis. The boundary for the final analysis will be derived accordingly from the pre-specified α-spending function such that the overall significance level across all analyses is maintained at 0.025.

The statistical properties of the group sequential design are summarized for DFS in Table 10-1 below.

Table 10-1 Simulated probabilities to stop for futility or efficacy at the interim or final DFS analysis

Scenario	Look	# DFS events	Simulated cumulative probabilities (%)		Simulated incremental probabilities (%)	
			Stop for efficacy	Stop for futility	Stop for efficacy	Stop for futility
Under H_{01} (HR=1)	1st IA (futility)	196	-	59.34	-	59.34
	Final	392	2.36	-	2.18	-
Under H_{a1} (HR=0.716)	1st IA (futility)	196	-	1.83	-	1.83
	Final	392	89.56	-	63.7	-
Under HR=0.8	1st IA (futility)	196	-	9.28	-	9.28
	Final	392	58.65	-	50.49	-

Note: Simulation is performed in East 6.4 with number of simulations = 10,000 and randomization seed = 1234

The interim analysis will be performed by an independent statistician (not involved with the conduct of the study). Further details will be described in the DMC charter. The results of the interim analysis will be provided to the DMC by the independent statistician.

10.7.2 Key secondary endpoint: Overall survival (OS)

A hierarchical testing procedure will be adopted and the statistical tests for OS will be performed only if the primary efficacy endpoint DFS is statistically significant.

[redacted]

A maximum of three analyses are planned for OS; at the time of the final analysis for DFS (provided DFS is statistically significant), at which point a total of approximately 318 (63%) deaths are expected, an additional IA for OS when a total of approximately 418 (83%) deaths are expected (expected 52 months from the date of the first subject being randomized), and a final analysis for OS when approximately 504 deaths are expected (expected 63 months from the date of the first subject being randomized).

An α-spending function according to Lan-DeMets (O'Brien-Fleming) as implemented in East 6.4 (Lan and DeMets 1983), independent of the one used for the DFS, along with the testing strategy outlined below will be used to maintain the overall type I error probability. This guarantees the protection of the 2.5% overall level of significance across the two hypotheses and the repeated testing of the OS hypotheses in the interims and the final analysis (Glimm 2010).

The trial allows for the stopping of the study for a superior OS result, provided the primary endpoint DFS has already been shown to be statistically significant favoring the test treatment arm. Further, the exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses.

The projected timing of interim analysis is summarized in Table 10-2.

At the time of final DFS analysis, both DFS and interim OS analysis will be performed by the Sponsor's clinical team. Investigators and subjects will remain blinded to study treatment and all subjects will continue to be followed for OS until the final OS analysis (or earlier if OS reaches statistical significance at any of the interim analyses).

The statistical properties of the group sequential design are summarized for OS in Table 10-2 below.

Table 10-2 Simulated cumulative power to stop for efficacy on overall survival at final DFS analysis or final OS analysis

Look	Months after randomization of the first subject (approximation)	# DFS Events	Cumulative power against a hazard ratio of 0.716	# OS Events	Cumulative power[b] against a hazard ratio of 0.776
1st DFS IA (futility)	27	196 (50.0%)	-	-	-
Final DFS	42	392 (100%)	89.56%	318 (63.1%)[a]	36.26%
OS IA	52	-	-	418 (82.9%)[a]	64.09%
Final OS	63	-	-	504 (100%)[a]	79.25%

a: To be performed only if the final DFS analysis is significant

b: Power conditional on DFS being significant

Simulations performed in East 6.4 with number of simulations = 10,000 and randomization seed =1234.

[redacted]

10.8 Sample size calculation

The sample size calculation is based on the primary variable DFS. The hypotheses to be tested and details of the testing strategy are described in Sections 10.4.2 and Section 10.7.1.

Based on available data, the median DFS in the placebo arm is expected to be around 48 months (Kelly 2015). It is expected that treatment with canakinumab will result in a 28.4% reduction in the hazard rate for DFS (corresponding to an increase in median DFS from 48 months to 67 months under the exponential model assumption).

Then, in order to ensure 90.4% power to test the null hypothesis: DFS hazard ratio = 1, versus the specific alternative hypothesis: DFS hazard ratio = 0.716, it is calculated that a total of 392 DFS events need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, subjects randomized to the two treatment groups in a 1:1 ratio, and a 2-look group sequential design with a Lan-DeMets (O'Brien-Fleming) α-spending function and a user-defined gamma function (with γ=-3) β-spending function to define a non-binding futility rule at the interim analyses, using an information fraction of 50% for the interim analysis (futility only) . Assuming that enrolment will continue for approximately 30 months at a rate of 50 subjects per month and a 5% yearly dropout rate by the time of the final DFS analysis, approximately 1500 subjects may be randomized to observe the targeted 392 DFS events at about 12 months after the randomization date of the last subject, i.e., 42 months after the randomization date of the first subject. It is required that all enrolled subjects have a minimal efficacy follow-up of 3 months to ensure all subjects have at least one post-baseline recurrence assessment. These calculations were made using the software package East 6.4.

10.9 Power for analysis of key secondary variables

OS, as the key secondary variable, will be formally statistically tested, provided that the primary variable DFS is statistically significant. The hypotheses to be tested and details of the testing strategy are provided in Section 10.5.1 and Section 10.7.2. Based on available data, the median OS in the placebo arm is expected to be approximately 5 years (Pignon 2008). In addition, the OS result presented in Kelly (2015) was not mature as the median was not reached at 5 years, but the overall trend indicates a median OS greater than 5 years. After taking these into consideration, the median OS for the placebo arm is assumed to be approximately 66 months. It is hypothesized that treatment with canakinumab will result in a 22.4% reduction in the hazard rate for OS, i.e., an expected hazard ratio of 0.776 (which corresponds to an increase in median 66 to 85 months under the exponential model assumption). Then, in order to ensure 80% power to test the null hypothesis: OS hazard ratio = 1, versus the specific alternative hypothesis: OS hazard ratio = 0.776, it is calculated that a total of 504 deaths need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, subjects randomized to the two treatment arms in a 1:1 ratio, and a 3-look group sequential design with a Lan-DeMets (O'Brien-Fleming) α-spending function using information fractions of 63%, 83% and 100%. Based on the same number of subjects that are planned to be enrolled in this study to provide sufficient power for the primary endpoint (i.e., 1500 subjects), and assuming losses to follow-up for OS of 3% yearly, it is estimated that these 504 deaths will be observed approximately 63 months after the randomization date of the first subject. Therefore the cut-off date for the final analysis of OS will be approximately 21 months

[redacted]

after the cut-off date for the final analysis of DFS. These calculations were made using the software package East 6.4.

10.10 Sample size consideration in the sub-study

Enrollment into the sub-study will end when the enrollment into the main study has been completed. This section explores the impact of different sample sizes on testing DFS hypotheses in biomarker subgroups.

It is assumed that canakinumab will result in a 28.4% reduction in hazard rate for DFS (hazard ratio of 0.716) in the biomarker subgroup of interest assessed at pre/post-surgery and approximately 50% enrolled subjects in the sub-study are expected to be randomized in the main study. Assuming an equal distribution of subjects across the biomarker subgroups of interest and a similar DFS event rate (~26%) from all randomized subjects is expected to be observed in the biomarker subgroup of interest, Table 10-3 shows the power to reject the null hypothesis H0: DFS hazard ratio = 1, versus the specific alternative hypothesis H1: DFS hazard ratio = 0.716 in the biomarker subgroup of interest for different sample sizes in the sub-study at a one-sided 2.5% level of significance without any multiplicity consideration for control of overall type 1 error.

Table 10-3 Power to reject the null hypotheses in the biomarker subgroup of interest for different sample sizes in the sub-study

Sample size in the sub-study	Number of subjects from sub-study randomized in the main study	Biomarker subgroup sample size	Number of DFS events in the biomarker subgroup	Power to reject the null hypothesis for DFS in the biomarker group
2000	1000	500	131	48%
1800	900	450	118	44%
1500	750	375	98	38%
1200	600	300	79	32%
1000	500	250	65	27%

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, 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 and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 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. 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.

11.3 Informed consent procedures

Eligible subjects 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 subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject 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 subject source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH E6 GCP guideline and regulatory requirements. Any changes to this ICF 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 subject will not reliably comply, they should not be entered in the study.

As per Section 2.7, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local heath authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial subject and person obtaining informed consent, etc.).

Additional consent form

Sub-studies and studies with an optional Exploratory Biomarker component will have a separate consent form covering those studies. This form will be adapted for each study based on a standard template used globally for all studies. These informed consent forms will be submitted for ethical approval together with the Study Protocol and the main informed consent form of the study. If a subject opts not to participate in the optional assessments, this in no way affects the subject's ability to participate in the main research study.

[redacted]

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. wwwclinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult subjects are posted on wwwnovartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric subjects within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (wwwicmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to wwwnovartis.com.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Patient Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples

[redacted]

of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (eCRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. Any change or correction to a paper eCRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic eCRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and subject records

The investigator must ensure anonymity of the subjects; subjects must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and subject enrollment log must be kept strictly confidential to enable subject identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of subjects at the site - prior to study start.

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 study

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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 Amendments to the protocol

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 subject 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 subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

[redacted]

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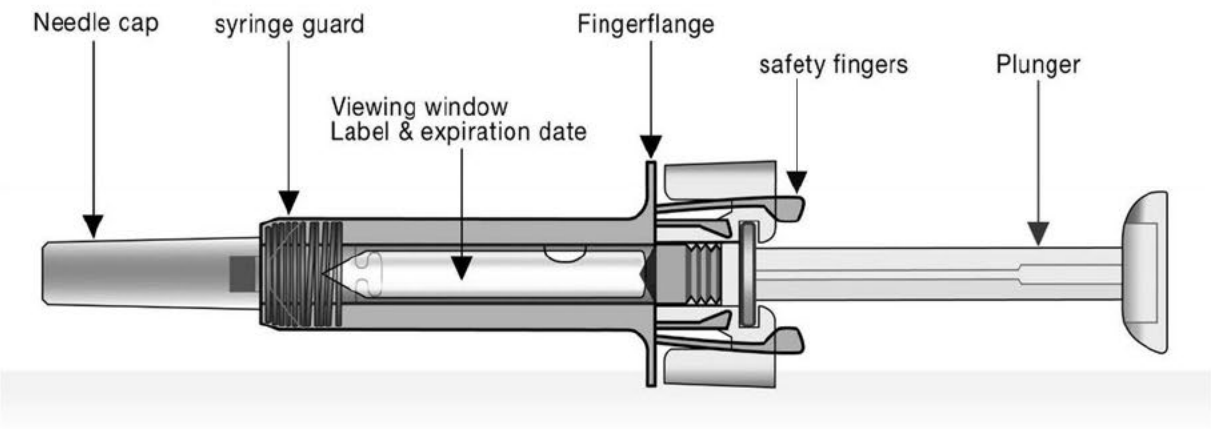
14 Appendices

14.1 Appendix 1: Instructions for use of the safety syringe

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

Parts of the safety syringe

This safety syringe consists of the actual prefilled syringe and a safety device type X100L (CE-marked and 510(k) K060743 cleared) from SafetySyringes, Inc.



This needle guard system is intended to aid in the protection of healthcare professionals, subjects who self-inject doctor prescribed medications, and individuals that assist self- injecting subjects form accidental needle sticks.

Important safety information

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

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

[redacted]

Storage of the safety syringe

1. Store the safety syringe sealed in its outer box in the refrigerator between 2°C and 8°C (36°F and 46°F). DO NOT STORE IT IN THE FREEZER AND PROTECT FROM LIGHT.
2. Remember to take the safety syringe out of the refrigerator and allow it to reach room temperature before preparing it for injection (15 to 30 minutes).
3. Do not use the safety syringe after the expiration date shown on the outer box or syringe label. If it has expired, return the entire pack to the pharmacy.

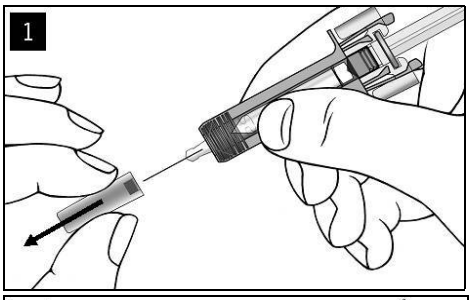
The injection site

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

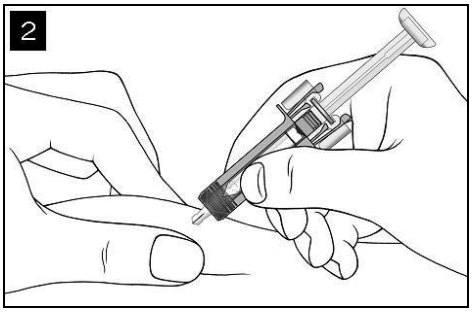
Preparing the safety syringe ready for use

1. Take the box containing the safety syringe out of the refrigerator and leave it unopened for about 15 to 30 minutes so that it reaches room temperature.
2. When you are ready to use the safety syringe, wash your hands thoroughly with soap and water.
3. Clean the injection site with an alcohol swab.
4. Remove the safety syringe from the outer box and take it out of the plastic wrapper.
5. Inspect the safety syringe. DO NOT USE if it is broken or if the liquid has a distinctly brown discoloration or contains particles. In all these cases, return the entire product pack to the pharmacy.

How to use the safety syringe



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



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

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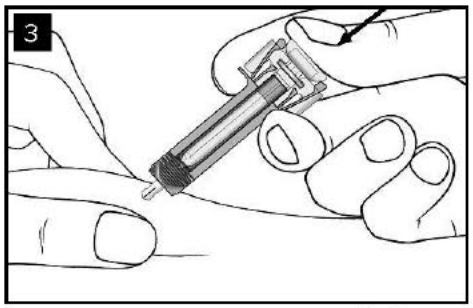
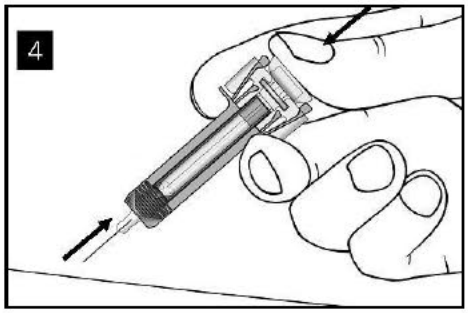
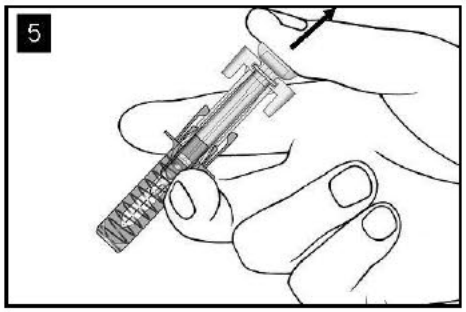


Holding onto the finger flange, **slowly** depress the plunger as far as it will go. If some drug leaks from the injection site, insert the needle further.

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



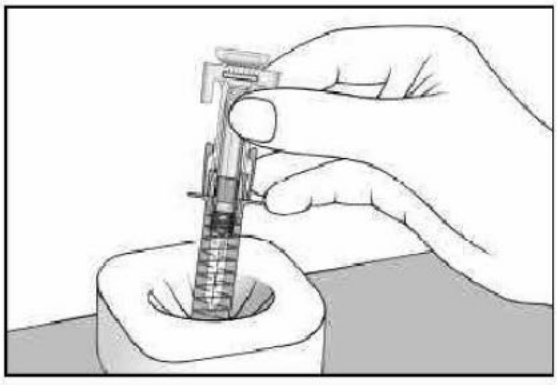
Keep the plunger fully depressed while you carefully lift the needle straight out from the injection site.



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

Disposal instructions

Dispose the used safety syringe immediately in a sharps container. For the safety and health of you and others, needles and used syringes **must never** be re-used.



14.2 Appendix 2: AJCC v.8 Prognostic Stage Groups (adapted from the AJCC Cancer Staging Manual 2017)

When T is...	And N is...	And M is...	Then the stage group is...
TX	N0	M0	Occult carcinoma
Tis	N0	M0	0
T1mi	N0	M0	IA1
T1a	N0	M0	IA1
T1a	N1	M0	IIB
T1a	N2	M0	IIIA
T1a	N3	M0	IIIB
T1b	N0	M0	IA2
T1b	N1	M0	IIB
T1b	N2	M0	IIIA
T1b	N3	M0	IIIB
T1c	N0	M0	IA3
T1c	N1	M0	IIB
T1c	N2	M0	IIIA
T1c	N3	M0	IIIB
T2a	N0	M0	IB
T2a	N1	M0	IIB
T2a	N2	M0	IIIA
T2a	N3	M0	IIIB
T2b	N0	M0	IIA
T2b	N1	M0	IIB
T2b	N2	M0	IIIA
T2b	N3	M0	IIIB
T3	N0	M0	IIB
T3	N1	M0	IIIA
T3	N2	M0	IIIB
T3	N3	M0	IIIC
T4	N0	M0	IIIA

[redacted]

T4	N1	M0	IIIA
T4	N2	M0	IIIB
T4	N3	M0	IIIC
Any T	Any N	M1	IV
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVA
Any T	Any N	M1c	IVB

[redacted]