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Novartis Institutes for BioMedical Research

ACZ885

Clinical Trial Protocol CACZ885X2206

A multiple-dose, subject- and investigator-blinded, placebo-controlled, parallel design study to assess the efficacy, safety and tolerability of ACZ885 (canakinumab) in pediatric and young adult patients with sickle cell anemia

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not be part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO& PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

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List of abbreviations

γ-GT	gamma-glutamyl transferase
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under curve
BMI	Body Mass Index
BUN	blood urea nitrogen
CAPS	cyropyrin-associated periodic syndromes
CINCA	chronic infantile neurological, cutaneous, articular syndrome
CFR	Code of Federal Regulation
CK	creatinine kinase
CO_2	carbon dioxide
COAR	Clinical Operations, Analytics & Regions
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CTC	Common Toxicity Criteria
CV	coefficient of variation
EDC	Electronic Data Capture
ELISA	enzyme-linked immunosorbent assay
EOS	End of study
EU	European Union
FCU	familial cold urticaria
FCAS	Familial Cold Autoinflammatory Syndrome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLM	generalized linear model

h	Hour
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hs-CRP	high-sensitivity C-reactive protein
Hydroxyurea	Hydroxyurea/hydroxycarbamide
i.v.	intravenous
IAC	Infection Adjudication Committee
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL	interleukin
IL-18BPa	interleukin-18 binding protein
IL-1RA	interleukin-1 receptor antagonist
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intention-to-treat
IUD	intrauterine device
LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal

LOCF	last observation carried forward
MAC	Malignancy Adjudication Committee
MAR	missing at random
MCID	Minimally clinical important difference
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMRM	Mixed-effect Model for Repeated Measures
MWS	Muckle Wells Syndrome
NOMID	neonatal-onset multisystem inflammatory disease

PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
POC	Proof of concept
RBC	red blood cell(s)
s.c.	subcutaneous
SAE	serious adverse event
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SCA	sickle cell anemia
sCR	serum creatinine
SD	standard deviation
sJIA	systemic juvenile idiopathic arthritis
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	tuberculosis
TBL	total bilirubin
TCD	Transcranial Doppler
TRAPS	TNF receptor-associated periodic syndrome
UK	United Kingdom
ULN	upper limit of normal
US	United States of America
VAS	visual analog scale
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WBC	white blood cell(s)
WHO	World Health Organization

Pharmacokinetic definitions and symbols

AUCinf	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
Cav,ss	The average steady state plasma (or serum or blood) concentration during multiple dosing
CL	The systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration [volume / time]
CL/F	The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time]
CLr	The renal clearance from plasma (or serum or blood) [volume / time]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Vss	The volume of distribution at steady state following intravenous administration [volume]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug" or "test substance"
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.

Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm

Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as 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, and does not allow analysis of already obtained biologic material

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Protocol synopsis

Protocol number	CACZ885X2206
Title	A multiple-dose, subject- and investigator-blinded, placebo-controlled, parallel design study to assess the efficacy, safety and tolerability of ACZ885 (canakinumab) in pediatric and young adult patients with sickle cell anemia.
Brief title	Study of efficacy, safety and tolerability of ACZ885 (canakinumab) in pediatric and young adult patients with sickle cell anemia.
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	This study is designed to assess if inhibition of IL-1β by canakinumab will reduce daily pain in association with attenuation of intravascular inflammation in pediatric and young adult patients with sickle cell anemia, therefore allowing further development of the compound for treatment of this disease population. A pediatric and young adult population (8-20 years of age) is chosen because the patients are more likely to be without significant accumulated, SCA-related co-morbidities and are most likely to benefit from the compound's mechanism of action. Moreover, canakinumab has been widely studied in inflammatory diseases involving pediatric populations that encompass the age range proposed in this study, with an estimated 528 pediatric patients <1 to 17 years exposed to canakinumab treatment in Novartis-sponsored interventional studies as of 30 June 2017. Among the inflammatory diseases involving pediatric patients for which canakinumab has received health authority approvals include sJIA and CAPS for patients ≥2 years and ≥4 years, respectively. The dose of canakinumab selected for the current proof-of-concept trial is 300 mg s.c. (4 mg/kg for patients ≤40 kg), monthly. This dosing regimen is predicted to achieve and maintain suppression of the inflammation over time, allowing for tissue repair and reductions in pain and crisis frequency. Stratification is planned for patients at treatment randomization according to presence or absence of concurrent hydroxyurea use because this standard-of-care therapy has potential therapeutic benefits against the disease, but its practical use in pediatric populations remains limited. The rationale for the additional safety visit 8 weeks after the final clinical assessment at Week 48 is to monitor for any potential, late appearing AEs after having terminated treatment. The opportunity for continued, open label treatment is provided in this study design to allow participants from the placebo-treated arm the option for receiving active treatment and for those in the active treatment group to continue on treatment, thus providing additional exposure data and evidence for sustained efficacy in this patient population in which canakinumab is envisaged as a long term treatment.

Primary Objective(s)	To determine the effect of canakinumab versus placebo on daily pain experienced by sickle cell anemia patients (Reduction of average daily pain VAS over the period of Week 8 to 12 as compared to baseline levels).
Secondary Objectives	- To determine the duration of effects of canakinumab versus placebo on daily pain experienced by SCA patients (Reduction of average daily pain VAS over 4-week intervals up to Week 24 as compared to baseline levels) - To determine the effect of canakinumab versus placebo on laboratory markers of inflammation (Week 12 versus baseline of: serum hsCRP, WBC count, Absolute counts of blood neutrophils, Absolute counts of blood monocytes). - To determine the effect of canakinumab versus placebo on laboratory and functional markers of hemolysis. - To determine the effect of canakinumab versus placebo on SCA-related days missed from school or work - To determine the effect of canakinumab versus placebo on reducing the need for acute blood transfusion - To assess the safety and tolerability of canakinumab in patients with SCA as measured by adverse events (AEs), including immunogenicity as indicated by the presence of anti-drug antibodies - To determine the PK of canakinumab in SCA patients
Study design	This study is an ambulatory-based study of 24 weeks duration followed by an additional 24-week open label phase and is subject- and investigator-blinded, randomized, placebo-controlled, parallel group, non-confirmatory to assess the clinical efficacy of canakinumab administered s.c. in 6 injections given 28 days apart (monthly injections). This study will randomize approximately 60 pediatric and young adult patients (targeting 48 completers) diagnosed with SCA who experience chronic or episodic pain, i.e., detectable average daily pain level over a 1-2 week screening period and ≥2 painful episodes in the past year of likely sickle cell etiology requiring analgesia and interfering with the patient's normal daily routine.
Population	This study will recruit patients, 8 to 20 years of age (both inclusive) with SCA.
Key Inclusion criteria	- Male and female subjects, 8-20 years of age (both inclusive) diagnosed with sickle cell anemia (HbSS) or sickle beta^0 thalassemia (documented by family studies, or analysis of either hemoglobin or DNA). - Patient's written informed consent from those ≥18 years of age must be obtained before any assessment is performed. Parent or legal guardian's written informed consent and child's assent, if appropriate, are required before any assessment is performed for patients < 18 years of age. - Detectable baseline of background or episodic pain measured by daily e-diary over 1 to 2 weeks during screening period as defined below: Average daily pain score ≥ 1 cm without analgesic use over a period of at least 7 days and/or, At least one episode of pain requiring analgesic use during a period of up to 14 days. - History of ≥2 vaso-occlusive pain episodes in the past year, as defined as pain with no other, non-sickle cell identifiable cause that requires analgesia and interferes with the patient's normal daily routine.

Key Exclusion criteria	- History of known anaphylaxis or hypersensitivity to canakinumab or any component thereof. - Ongoing or treatment within the past 3 months with red blood cell transfusion therapy, or have evidence of iron overload requiring chelation therapy. - Transcranial Doppler ultrasound in the past year or at screening demonstrating velocity in middle or anterior cerebral or internal carotid artery ≥200 cm/sec. Note, transcranial Doppler (TCD) assessment is only required in patients for whom the trans-temporal acoustic window is sufficient for imaging the cranial arteries. - Administration of any other blood products within 3 weeks prior of screening visit.
Study treatment	The dose of canakinumab selected for the current proof-of-concept trial is 300 mg s.c. monthly (4 mg/kg for patients ≤40 kg),
Efficacy/PD assessments	- Reduction of average daily pain VAS over the period of Week 8 to 12 as compared to baseline levels - Reduction of average daily pain VAS over 4-week intervals up to Week 24 as compared to baseline levels - Serum hsCRP, WBC count, absolute counts of blood neutrophils, absolute counts of blood monocytes, hemoglobin concentration, reticulocyte count, haptoglobin, LDH, bilirubin (total, direct and indirect), Commercially Confidential Information
Key safety assessments	- Adverse events, - Commercially Confidential Information
Other assessments	Commercially Confidential Information
Data analysis	The post-baseline average daily pain VAS (visual analog scale) will be calculated for each dose from the start of the dose till the day before the next dose, i.e., in an averagely 4-week interval (e.g., Week 0-4, Week 4-8, etc., depending on the actual dosing days). The baseline average pain VAS will be calculated as the average of daily pain scores from screening up to pre-dosing over a period of at least 7 days. Reduction from baseline in the average daily pain VAS, i.e., baseline minus post-baseline, will be analyzed using a Bayesian model for repeated measures using Proc MCMC in SAS. The model includes baseline average daily pain score as a continuous covariate; treatment group, time and hydroxyurea use history (Yes/No) as fixed factors. Interactions of time by treatment group and time by baseline covariates will also be included in the model. Non-informative priors will be used for the fixed effects and weakly informative prior, for the covariance. Unstructured covariance structure will be used and other covariance structure will be investigated if there is convergence problem. Interaction of hydroxyurea use and treatment group will be explored via visualizations; if substantial interaction is suspected it will be further explored by including this interaction term in the whole model. A comparison of canakinumab 300 mg s.c. versus placebo for the period of Week 8-12 is of primary interest. Data up to Week 12 will be included in the primary model. Bayesian posterior probabilities will be used to assess the following PoC criteria as a guidance for decision making: Prob (the reduction of average pain score over the period of Week 8-12 in canakinumab is greater than Placebo) > 90%, and Prob (the reduction of average pain score over the period of Week 8-12 in

	canakinumab is greater than Placebo by 1) > 50%. The target difference of 1 is chosen based on the literature search on the Minimally Clinical Important Difference (MCID) in pain studies. Commercially Confidential Information Data up to Week 24 will also be analyzed with the same model specifications when there are at least about 50% completers at Week 24 and also upon the study completion. Pain data in the open label when available will also be summarized, visualized and explored in appropriate statistical models, to evaluate the maintenance of the efficacy in patients randomized to canakinumab group and/or improvements in patients randomized in placebo group. Patients who have missed two consecutive dosing or more in the blinded treatment period or have other protocol deviations severely affecting the evaluation of efficacy will be excluded in the primary efficacy analysis for the blinded period. This is the primary PD analysis set.
Key words	ACZ885, canakinumab, adolescent, sickle cell anemia

1 Introduction

1.1 Background

Sickle cell anemia (SCA)

SCA is a life-long disease with high morbidity and mortality. This inherited disease is the most common hemoglobinopathy and is caused by a single amino acid change in the β-globin chain that results in structurally abnormal hemoglobin S, or by compound heterozygosity for hemoglobin S and another β-globin chain abnormality, typically hemoglobin C or β-thalassemia. These mutations lead to abnormally shaped sickle cell erythrocytes with reduced membrane elasticity with increased propensity for lysis and adherence. Heterozygous individuals carrying one copy of the mutation (sickle cell trait) usually have no overt disease, but those homozygous for the mutation can experience disease severity and potential complications to varying extents, dependent on the proportion of red blood cells affected, other, coexisting conditions such as G6PD deficiency or thalassemia, and exposure to environmental factors such as infection, dehydration and acidosis that favor sickling.

There are an estimated 312,000 people homozygous for hemoglobin S (hemoglobin SS, HbSS) born each year throughout the world (Saraf et al 2014). Global distributions of newborns with the disease are 60% in sub-Saharan Africa, 20% in Arab-Indian regions, 7% in the Americas and 5% in Eurasia. There are about 20-25 million individuals world-wide who have homozygous sickle cell disease, including 12 -15 million in sub-Saharan Africa, 5-10 million in India and about 3 million scattered about elsewhere in the world. Due to the similar historical distribution patterns of malaria and of hemoglobin S, it has been proposed that protection from malaria provided a heterozygote advantage for these mutations in selected populations. Subsequent migration patterns have distributed sickle cell genes into regions not endemic for malaria. About 8% of African Americans carry the sickle gene and 100,000 live with SCA. However, they are responsible for >70,000 annual hospitalizations (Kauf et al 2009). Among SCA patients the median age at death is 42 years in Western society and half that age in less developed countries.

Clinical manifestations of the disease include chronic inflammation, acute and chronic pain, fatigue and chronic hemolytic anemia with recurrent vaso-occlusive crises. Thus, patients experience chronic signs and symptoms of their disease throughout life, punctuated by episodic crises, together resulting over time in severe end-organ damage and early mortality. Children and adults with SCA have an overall reduced quality of life. Chronic fatigue also plays a role in reduced quality of life in SCA patients and is associated with acute care visits for pain as well as school absences and missed caregiver workdays (Dampier et al 2010, Panepinto et al 2014). Other known complications of the disease include stroke, osteonecrosis, nephropathy, pulmonary disease, retinopathy, priapism and reduced cognition. The spleen is frequently affected early in life due to repeated infarctions, leading to increased susceptibility to infections by encapsulated organisms.

Treatment options for SCA are quite limited, with hydration, analgesia and antibiotics used for management of acute SCA crises. Hydroxyurea (ribonucleotide reductase inhibitor), first synthesized in 1869, is approved in the US and in the EU for SCA and is used to reduce frequency of crises by increasing the proportion of fetal hemoglobin over the mutated sickle form. However, hydroxyurea remains underutilized by SCA patients and their physicians due to uncertainties regarding associated toxicities. This cytostatic drug has a wide range of potential AEs that include bone marrow toxicity and potential increased leukemia risks and thus requires close monitoring. L-glutamine (Endari™) is approved in the US to reduce the acute complications of SCA in adult and pediatric patients 5 years and older. Another SCA therapy is frequent blood transfusions to reduce the proportion of sickle-prone RBCs in circulation. The only known potential cure for SCA is bone marrow transplantation which has proven effective in children but its potential long term toxicities limit use to only the most severely affected patients. Therefore, alternative therapeutic targets and disease mechanisms should be considered in this disease.

Evidence for chronic intravascular inflammation in sickle cell disease

Due to increased hemolysis of the abnormal, sickled red blood cells, SCA patients have constitutively high levels of circulating hemoglobin/heme that exhausts the body's protective scavenger capacity, driving acute on chronic inflammation under sterile or infectious conditions. High levels of C-reactive protein (CRP) and other inflammation mediators such as IL-1β, IL-6, IL-17, IL-18 and TNF-α are common in SCA. Increased levels of IL-1β and IL-18 trigger endothelial cell activation, upregulation of adhesion molecules and neutrophil activation (Dinarello 1999; Morel et al 2001; Gerdes et al 2002). Acute crises arise from increased adhesive interactions between sickled RBCs and leukocytes with endothelial cells, triggered by stressors such as dehydration or otherwise mild viral infections, causing vascular obstruction and tissue ischemia. A vicious, positive feedback cycle of inflammation ensues, resulting in marked pain and end organ damage.

The inflammasome is a multiprotein oligomer that is expressed in myeloid cells as a component of the innate immune system. Inflammasomes can be triggered by a variety of activators and processes, resulting in an inflammatory cascade that includes cleavage by caspase-1 of pro-IL-1β and pro-IL-18 into their active forms, along with triggering of other inflammatory processes. Over the last few years, there has been an increasing body of literature about the efficacy of targeting IL-1β in a wide spectrum of autoinflammatory conditions. Autoinflammatory disorders can be distinguished from autoimmune disorders by disease mechanisms involving innate immune regulation of cytokines and neutrophilic inflammation rather than adaptive immune responses involving antibodies and lymphocytes. Inflammasome-mediated diseases include rare orphan diseases classified together within the condition of hereditary periodic fevers. Another disease in which the inflammasome plays a key role is gouty arthritis. These conditions have in common either conditions or mutations that result in increased inflammasome activation, resulting in chronically recurring inflammation.

Sickle cell anemia as an inflammasome-mediated disease

Recent literature evidence has identified SCA to have a strong inflammasome-driven component via high rates of constitutive intravascular hemolysis that overwhelm the scavenger capacity of the body for heme and free iron, resulting in chronic activation of endothelial cells and vascular inflammation. In mouse models, heme induces IL-1β production and neutrophil migration dependent on caspase-1 cleavage, thus demonstrating inflammasome activation (Dutra et al 2014). In the same report, the hemolysis-induced lethality in an animal model was greatly reduced in Nlrp3-, Asc- and caspase-1-deficient mice, indicating inflammasome involvement. Transgenic SCA animal models largely recapitulate human pathophysiology, with subclinical inflammation and increased neutrophil counts as well as elevated soluble vascular adhesion molecules (Cain et al 2012). Anti-IL-1β antibody treatment in another transgenic SCA mouse model markedly ameliorated intravascular flow impedance induced by hypoxia (Kaul and Gram 2011).

Therapeutic targeting of IL-1β in sickle cell disease

IL-1β is recognized as one of the principal pro-inflammatory cytokines in a variety of inflammatory conditions, including those involving autoinflammation and the inflammasome (Church et al 2008). This cytokine is produced by a variety of cell types, particularly mononuclear phagocytes, in response to injury, infection and inflammation.

ACZ885 (canakinumab) is a high affinity, fully human, monoclonal anti-human interleukin-1β (IL-1β) antibody of the IgG1/κ isotype that is designed to bind to human IL-1β, blocking the interaction of this cytokine to its receptors, thus functionally neutralizing the bioactivity of this cytokine.

Canakinumab is currently registered in more than 70 countries worldwide under the name Ilaris®. Depending on countries, Ilaris is approved for treatment of adults and children aged 2 years and older that have a condition known as cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome (FCAS) / Familial Cold Urticaria (FCU), Muckle-Wells syndrome (MWS) and Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA). Additional monogenetic periodic fever syndromes for which Ilaris® has received approvals include tumor necrosis factor receptor-associated periodic syndrome (TRAPS), colchicine-resistant/intolerant familial Mediterranean fever (crFMF) and hyper-Immunoglobulin D Syndrome with periodic fever syndrome (HIDS)/ Mevalovate Kinase Deficiency (MKD) (Rigante 2016). Ilaris® is also approved for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in children 2 years of age and older and in Europe for the symptomatic treatment of acute gouty arthritis attacks. For further details please refer to the Investigators Brochure (IB).

The above evidence supports that inflammasome activity is constitutively upregulated in sickle cell anemia patients and may play a role in disease activity. Thus, IL-1β pathway interruption with canakinumab is anticipated to confer therapeutic benefit.

1.2 Nonclinical data

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1.2.1 Teratogenicity and reproductive toxicity data

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1.3 Clinical data

1.3.1 Human safety and tolerability data

As of 30 June 2017, an estimated 10,939 patients, of which 528 pediatric patients aged <1 to 17 years, have received canakinumab treatment in 74 Novartis-sponsored investigational clinical trials and 16 third party, investigator-initiated trials in a wide spectrum of diseases where IL-1β plays a role, such as cryopyrin-associated periodic syndromes (CAPS), mild asthma, psoriasis, wet age-related macular degeneration (AMD), gouty arthritis, type 2 diabetes mellitus, atherosclerosis, rheumatoid arthritis (RA), and systemic juvenile idiopathic arthritis (sJIA). Health authority approvals for Ilaris have been granted for monogenetic periodic fever syndromes, including CAPS, TRAPS hyper-Immunoglobulin D Syndrome with periodic fever syndrome (HIDS)/ Mevalovate Kinase Deficiency (MKD), colchicine-resistant/intolerant familial Mediterranean syndrome (crFMF), gout and sJIA. The post-

marketing cumulative patient exposure since the first launch of the product is estimated to be approximately 15,260 patient treatment-years as of 30 June 2017 year. The doses administered i.v. ranged from 0.3 mg/kg to 10 mg/kg or a fixed dose of 600 mg, and from 0.5 mg/kg to 9 mg/kg s.c. or fixed doses of 5 mg to 300 mg s.c. ACZ885 has a long half-life averaging approximately 4 weeks in man and monthly s.c. dosing of 4 mg/kg up to 300 mg is approved by the FDA and EMA for sJIA. The frequency of dosing ranged from a single dose to quarterly repeated administration. Pediatric patients and those patients with a severe CAPS phenotype may require higher than usual doses to attain full clinical response, and current labeling for canakinumab allows for dose escalation up to a maximum of 8 mg/kg for patients ≤40 kg and to 600 mg for patients >40 kg. Patients with systemic juvenile idiopathic arthritis (SJIA) also tend to require higher dosing of canakinumab for adequate response. These indications encompass a relatively comparable patient population to the ACZ885X2206 patient population in terms of age range and inflammatory levels. In registration and post-registration studies for canakinumab in this indication, there were no differences observed in the incidence of overall AEs across the different dosing groups, including those receiving either 150 mg or 300 mg s.c. monthly.

Studies in adult RA patients have been treated with 300 mg s.c. up to 184 weeks (studies CACZ885A2201, -E1 and -E2) at every 2 weeks for the first 12 weeks and every 4 weeks thereafter. The 300 mg dosing regimen was well-tolerated, without dose-dependent differences in AE incidence compared to every 4 weeks s.c. dosing of 150 mg.

Overall, the development program with ACZ885 has demonstrated a good safety and tolerability profile as evidenced by 1) a low number of study discontinuations for AEs, predominantly mild injection site reactions, and 2) no specific target organ toxicity. The AE profile is characterized by non-specific gastrointestinal and central nervous system events and infections predominantly of the upper respiratory tract, in some instances serious, with all infections responding to standard therapy. The details of the SAEs and AEs of the completed studies and relevant details of the SAEs of the ongoing studies are summarized in the latest version of the IB. Adverse events in unblinded studies ranged from mild-to-moderate in severity and include upper respiratory tract infections, nasopharyngitis and otitis, headache, nausea, diarrhea, and asthenic conditions. So far the maximum median duration of exposure to canakinumab is more than 4 years for the first 4 MWS patients enrolled in the CACZ885A2102 trial.

Similar to patients with monogenetic periodic fever syndromes, patients suffering from sickle cell anemia also have chronic inflammation and elevated serum levels of C-reactive protein and IL-1β (Akohoue et al 2007; Qari et al 2012) with recurrent periodic crises involving further, elevations of inflammation and serum CRP (Mohammed et al 2010; Kanavaki et al 2012). In a recently completed, large clinical trial involving pediatric and adult patients with periodic fever syndromes (CACZ885N2301), insufficient or non-response to initial canakinumab dosing at 150 mg resulted in further dose escalation to 300 mg/month in 16% of patients with crFMF, 32% of patients with HIDS and 36% of patient with TRAPS. In those patients, canakinumab dosed at 300 mg s.c. monthly was shown to bind additional IL-1β along with increased responder rates over rates observed with monthly s.c. dosing at 150 mg (i.e., crFMF +9.7%, HIDS +21.6%, TRAPS +27.3%). Similar improvements with increased monthly dosing of 300 mg versus 150 mg were also seen in secondary outcomes (i.e., physician global assessment of disease activity, serum reductions of acute phase

reactants). Thus, these results suggest that canakinumab dosing at 300 mg binds additional target and is more clinically effective than 150 mg dosing in patients with more severe inflammation.

1.3.2 Human pharmacokinetic data

Canakinumab has the expected pharmacokinetics of an IgG1-type antibody with a low volume of distribution (VSS=6.0 L) and low clearance. The serum clearance (CL) of canakinumab varied according to body weight (e.g., CL=0.174 L/day in a CAPS patient of body weight 70 kg, 0.11 L/day in a SJIA patient of body weight 33 kg and 0.23 L/day in a gout patient of body weight 93 kg). Half-lives vary between 21 and 30 days. Within the dose range studied, the pharmacokinetics of canakinumab were linear. The systemic exposure parameters, AUC and Cmax, increase in proportion to dose over the dose range of 0.30 to 10.0 mg/kg given as i.v. infusion and from 150 mg to 300 mg when administered as an s.c. injection. The absolute bioavailability of s.c. canakinumab is 70%. After accounting for body weight differences, no clinically significant differences in the pharmacokinetic properties of canakinumab were observed between CAPS, SJIA and gouty arthritis patients. Furthermore, with body weight-based dosing, canakinumab administered in pediatric indications (e.g., CAPS and SJIA) was observed to be similar in various age subgroups. For instance, in SJIA patients, exposure parameters corrected for body weight (such as AUC and Cmax) were comparable across age groups from 2 to <20 years following subcutaneous administration of canakinumab 4 mg/kg every 4 weeks. A mathematical model to characterize the binding kinetics of canakinumab to IL-1β has been created. The model successfully fits the patient data and allows estimation of canakinumab clearance and volumes of distribution, together with IL-1β rate of release and half-lives.

1.3.3 Human pharmacodynamic data

Canakinumab binds to and inactivates IL-1β and blocks downstream events of IL-1β signaling, including IL-1β production, IL-1β pathway-related gene activation, elevation of acute phase proteins, such as serum amyloid A (SAA) and C-reactive protein (CRP), and mobilization of neutrophils and platelets from bone marrow.

Normally undetectable, serum IL-1β becomes detectable in humans when complexed with canakinumab. These IL-1β/canakinumab complexes are biologically inactive and have been utilized in all clinical studies as a surrogate PD marker because their increase reflects the reduction of free IL-1β levels caused by binding to canakinumab.

1.4 Study purpose

This study is designed to assess if inhibition of IL-1β by canakinumab will reduce daily pain in association with attenuation of intravascular inflammation in pediatric and young adult patients with sickle cell anemia, therefore allowing further development of the compound for treatment of this disease population.

2 Study objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	*Endpoints related to primary objective(s)*
• To determine the effect of ACZ885 versus placebo on daily pain experienced by sickle cell anemia patients	• Reduction of average daily pain VAS over the period of Week 8 to 12 as compared to baseline levels

2.2 Secondary objective(s)

Secondary objective(s)	*Endpoints related to secondary objective(s)*
• To determine the duration of effects of canakinumab versus placebo on daily pain experienced by SCA patients	• Reduction of average daily pain VAS over 4-week intervals up to Week 24 as compared to baseline levels

• To determine the effect of canakinumab versus placebo on laboratory markers of inflammation	• Week 12 versus baseline of:
	  • Serum hs-CRP
	  • WBC count
	  • Absolute counts of blood neutrophils
	  • Absolute counts of blood monocytes

• To determine the effect of canakinumab versus placebo on laboratory and functional markers of hemolysis	• Week 12 versus baseline of:
	  • Hemoglobin concentration
	  • Reticulocyte count
	  • Haptoglobin
	  • LDH
	  • Bilirubin (total, direct and indirect)
	  • Oxygen percent saturation (SaO2)

• To determine the effect of canakinumab versus placebo on SCA-related days missed from school or work	• Number of days absent from school or work due to pain as recorded by daily e-diary
• To determine the effect of canakinumab versus placebo on reducing the need for acute blood transfusion	• The rate of SCA-related acute transfusion
• To assess the safety, including immunogenicity, and tolerability of canakinumab in patients with SCA as measured by adverse events (AEs)	• Adverse events in patients taking ACZ885 compared to placebo up to a total of 56 weeks treatment.
• To determine the PK of ACZ885 in SCA patients	• Serial serum PK determinations in patients with SCA

2.3 Exploratory objective(s)

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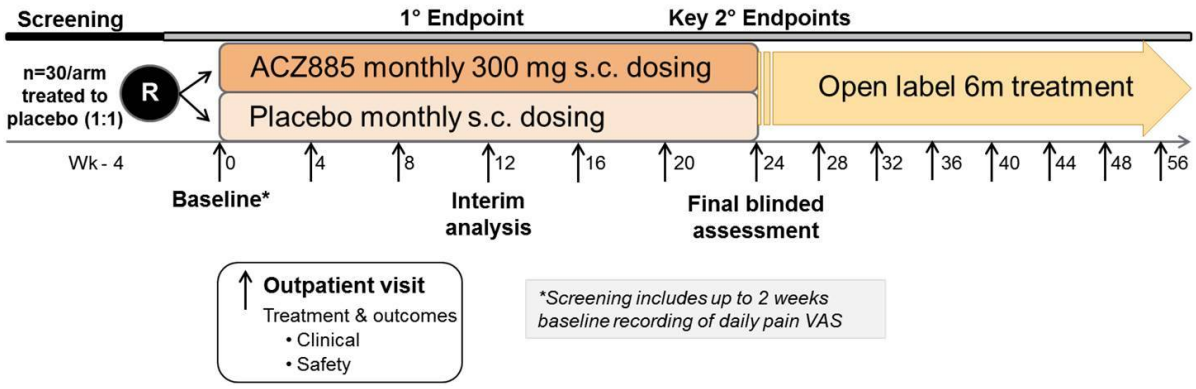
3 Investigational plan

3.1 Study design

This study (Figure 3-1) is an ambulatory-based study of 24 weeks duration followed by an additional 24-week open label phase and is subject- and investigator-blinded, randomized, placebo-controlled, parallel group, non-confirmatory to assess the clinical efficacy of canakinumab administered s.c. in 6 injections given 28 days apart. This study will randomize approximately 60 pediatric and young adult patients (targeting 48 completers of 8 to 20 years old) diagnosed with SCA who experience chronic or episodic pain, i.e., detectable average daily pain level over a 1-2 week screening period and at least 2 painful episodes in the past year of likely sickle cell etiology requiring analgesia and interfering with the patient's normal daily routine.

Figure 3-1 Study design



Acceptable prior established background therapy includes hydroxyurea and supportive antibiotic and analgesic medications. Patients will be randomized to either ACZ885 treatment or placebo treatment in a 1:1 ratio, with treatment stratification based on concurrent hydroxyurea therapy (yes/no).

Subjects who are prematurely withdrawn from the study for reasons other than safety or lack of efficacy will be replaced on a case-by-case basis. Re-screening of subjects may be allowed under the guidance of the Sponsor's medical expert.

For each subject, there will be a maximum 28-day screening period that will include recording of daily pain frequency and intensity by e-diary for at least 1 week.

Subjects who meet the eligibility criteria at screening will undergo evaluation of full baseline clinical and biomarker assessments prior to first dose administration. The screening daily pain results will be used to derive the baseline value for this primary endpoint of average daily pain. All safety evaluations must be available prior to dosing and results must demonstrate all eligibility criteria are met. Enrolled subjects will be randomized at a 1:1 ratio to receive treatment with either canakinumab or placebo with stratification based on concurrent hydroxyurea therapy. On Day 1, monthly s.c. dosing with canakinumab will begin at 4 mg/kg for patients weighing ≤ 40 kg and 300 mg for all other patients. Patients in the placebo treatment arm will be injected in a like manner with placebo. All patients will return to the study centers for safety checks on a monthly basis when they will receive treatment with either canakinumab or placebo. Additionally, patients will undergo clinical and laboratory evaluations as outlined in the Assessment Schedule every 28 days. The final blinded dosing will take place on Week 20, followed by blinded clinical assessments at Week 24. Patients from both study arms are then offered optional, open label monthly dosing of ACZ885 for an additional 24 weeks (Weeks 24-48), with clinical outcomes again assessed according to the Assessment schedule. Patients return for the end of study (EOS) visit at Week 56. For patients who choose not to participate in the optional, open label portion of the study, or for patients stopping treatment early for any other reason, an EOS visit will occur approximately 8 weeks after last dose received.

The EOS for an individual patient is defined as the EOS visit described above, which will occur approximately 8 weeks after last dose received. The global EOS is defined as the EOS visit of the last patient in the trial performing the EOS.

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A follow-up visit or phone call for SAEs must be performed 8 weeks following end-of-treatment visit or early discontinuation, or 8 weeks after last injection of study drug, whichever is later. If anaphylactic reactions occur after injection, two more immunogenicity samples (at the time of the event and 8 weeks later) need to be taken.

3.2 Rationale of study design

A randomized, placebo-controlled, subject and investigator blinded approach is used to eliminate potential bias in reporting safety and clinical efficacy data in this first exploratory study in SCA patients.

A pediatric and young adult population is chosen because those patients are more likely to be without significant accumulated, SCA-related co-morbidities and are most likely to benefit from the compound's mechanism of action. Moreover, canakinumab has been widely studied in inflammatory diseases involving pediatric populations that encompass the age range proposed in this study, with an estimated 528 pediatric patients <1 to 17 years exposed to

canakinumab treatment as of 30 June 2017. Inflammatory diseases involving pediatric patients for which canakinumab has received health authority approvals include sJIA and CAPS for patients ≥2 years and ≥4 years, respectively. Because levels of inflammation tend to increase during the course of childhood in SCA patients, this initial, early phase study will focus on pediatric and young adult patients of ages 8-20 years to increase the likelihood of detecting beneficial effects with an anti-inflammatory intervention.

Stratification is planned for patients at treatment randomization according to presence or absence of concurrent hydroxyurea use because this standard-of-care therapy has potential therapeutic benefits against the disease, but its practical use in pediatric populations remains limited.

High-sensitivity C-reactive protein (hs-CRP) is a marker that directly correlates with long term morbidity (van Beers et al 2015) and is part of this study's inclusion criteria. The hs-CRP threshold value of ≥1.0 mg/L used in this study's inclusion criteria is based on evidence from the literature that the 25-75 percentile value range of hs-CRP across a large, cross-sectional African American adolescent population aged 10-15 years is 0.1-1.2 mg/L (Ford et al 2003). In contrast, the 25-75 percentile value range of hs-CRP in children with HbSS/HbSβ^0thal ranged from 1.02-5.3 mg/L (Krishnan et al 2010). Importantly, the sickle cell variant HbSC in this study had lower hs-CRP values of 0.3-1.2 mg/L, with correspondingly reduced severity of anemia and other clinical manifestations of the disease. In a second report (Akohoue et al 2007) serum CRP values of the majority of HbAA adolescents (89%) were either <0.5 mg/L or not detectable, while in the steady-state HbSS adolescents, 34% had CRP levels ranging between 1-5 mg/L and >50% had CRP concentrations averaging 15.6 mg/L (5.7-52.6). Thus, the use of hs-CRP ≥1.0 mg/L in this study's inclusion criteria will ensure that enrolled patients have a minimal threshold of inflammation, an important therapeutic target of canakinumab.

The rationale for the additional safety visit 8 weeks after the final clinical assessment at Week 48 is to monitor for any potential, late appearing AEs after having terminated treatment. More information may be found in the Investigator’s Brochure.

The opportunity for continued, open label treatment is provided in this study design to allow participants from the placebo-treated arm the option for receiving active treatment and for those in the active treatment group to continue on treatment, thus providing additional exposure data and evidence for sustained efficacy in this patient population in which canakinumab is envisaged as a long term treatment.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

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3.4 Rationale for choice of comparator

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3.5 Rationale for choice of background therapy

Not applicable.

3.6 Purpose and timing of interim analyses/design adaptations

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3.7 Risks and benefits

Canakinumab has not been previously administered with therapeutic intent to patients with sickle cell anemia. Therefore, no statement can be made at this time on the actual clinical benefits of canakinumab in this patient population. However, given the mechanism of action of canakinumab and the relevant inflammatory pathways involving IL-1β as discussed in the background (Section 1.1), there is a reasonable expectation that a therapeutic response can be achieved with the compound in patients with sickle cell anemia.

Sickle cell anemia patients are at increased risk for infection, in part due to functional hyposplenism or from undergoing splenectomy (Booth et al 2010). This increased infection risk is primarily confined to very young children with the disease and is a major cause of early mortality from the disease. The main pathogen of concern is *S. pneumoniae*, and risk for invasive streptococcal disease in SCA patients drops markedly with age. Preventative measures are considered the key strategy in management of SCA infection risks. Optimal management of asplenic individuals includes life-long penicillin prophylaxis and keeping vaccinations up-to-date. Additional preventative measures include meticulous attention to hand washing, cooking food thoroughly, keeping perishable foodstuffs refrigerated, and avoiding contamination. Monitoring for early detection of infections is also important, with a low threshold for use of antibiotics.

Hydroxyurea, approved for SCA in the EU and US, is a mutagenic chemotherapy drug associated with bone marrow toxicity that requires close monitoring of blood counts and early recognition and treatment of infections. Thus there is precedence for the application of an immune suppressive treatment in this patient population.

Overall, the development program with canakinumab has demonstrated a good safety and tolerability profile as evidenced by a low number of study discontinuations for AEs, predominantly mild injection site reactions and no specific target organ toxicity. The AEs profile is characterized by non-specific gastrointestinal and central nervous system events, and infections predominantly of the upper respiratory tract and urinary tract infections, in some instances serious, with all infections responding to standard therapy. Patients may also experience reduction in leukocyte counts and thus will require close monitoring of their counts, in particular when receiving concomitant treatment with hydroxyurea. Treatment with canakinumab has a theoretically increased risk for opportunistic infections such as *M. tuberculosis*, but the actual frequency remains unknown.

The available toxicology, efficacy, safety, tolerability, overall low incidence of immunogenicity (as represented by the presence of treatment-emergent anti-drug antibodies) and preliminary efficacy data in MWS, RA, sJIA and gouty arthritis, further support the clinical development of canakinumab in diseases in which IL-1β is likely to have a predominant role. However, since preventing IL-1β receptor signaling may alter immunologic responsiveness in unanticipated ways, patients receiving ACZ885 will be closely monitored for clinical and laboratory indicators of immune suppression and immune dysregulation, such as infection including opportunistic infections (recognizing that blocking IL-1β may mask fever and blunt the inflammatory response to infection), blood cells count abnormalities (including neutropenia), and development of malignancies, autoimmune manifestations and hypersensitivity reactions.

Women of child bearing potential should be informed that taking the study drug 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 and up to 3 months after the last dose. If there is any question that the subject will not reliably comply, they should not be entered in the study.

There may be unknown risks of canakinumab which may be serious and/or unforeseen.

3.7.1 Blood sample volumes

A maximum of 189 mL of blood is planned to be collected over a period of 12 months, from each subject as part of the study. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

Timings of blood sample collection are outlined in the Assessment Schedule, Section 8.1.

A summary blood log is provided in the Site Operations Manual, together with instructions for all sample collection, processing, storage and shipment information.

See Section 8.9 regarding the potential use of residual samples.

4 Population

This study will recruit patients ages 8 to 20 years of age (both inclusive) with SCA, including hemoglobin SS and hemoglobin S-β^0 thalassemia, as determined by family studies, hemoglobin or DNA analyses. A total of approximately 60 patients will be randomized to participate in the study. Re-evaluation of the sample size based on the variability observed on the primary endpoint and the discontinuation rate may be performed when the study approaches the first IA and the total enrollment will be capped at 90 (Section 11.7).

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order for the study population to be representative of all eligible subjects.

Subject selection is to be established by checking through all inclusion/exclusion criteria at screening and first baseline prior to the first injection. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criterion excludes a subject from enrollment into the study.

Patient re-screening will be allowed in the study in the event of a delay in treatment, e.g., in the event of a washout period of more than 28 days.

4.1 Inclusion criteria

SCA patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Male and female subjects ages 8-20 years of age (both inclusive) diagnosed with sickle cell anemia (HbSS) or sickle beta^0 thalassemia (documented by family studies, or analysis of either hemoglobin or DNA).
2. Patient's written informed consent from those ≥18 years of age must be obtained before any assessment is performed. Parent or legal guardian's written informed consent and child's assent, if appropriate, are required before any assessment is performed for patients < 18 years of age.
3. Detectable baseline of background or episodic pain measured by daily e-diary over 1 to 2 weeks during screening period as defined below:
   - Average daily pain score ≥ 1 cm without analgesic use over a period of at least 7 days and/or,
   - At least one episode of pain requiring analgesic use during a period of up to 14 days.
4. History of ≥2 vaso-occlusive pain episodes in the past year, as defined as pain with no other, non-sickle cell identifiable cause that requires analgesia and interferes with the patient's normal daily routine.
5. Patients on hydroxyurea therapy need stable dosing >60 days prior to screening without signs of hematological toxicity and intention to remain on hydroxyurea therapy throughout the initial 6-month treatment period.
6. Screening hsCRP level ≥ 1.0 mg/L.
7. Full immunization status according to local guidelines against pneumococcus.
8. Able to communicate well with the investigator and to understand and comply with the requirements of the study.

4.2 Exclusion criteria

SCA patients fulfilling any of the following criteria are not eligible for inclusion in this study:

1. History of anaphylactic reaction or known hypersensitivity to canakinumab, or any component thereof.
2. Past history of invasive serious pneumococcal disease, including sepsis, bacteremia, and/or meningitis.
3. Ongoing or treatment within the past 3 months prior to screening with red blood cell transfusion therapy, or have evidence of iron overload requiring chelation therapy.
4. Administration of any other blood products within 3 weeks prior screening visit.
5. Uncontrolled liver disease or renal insufficiency, as defined by the following:
   elevated alanine aminotransferase (ALT) ≥ 3x ULN (if ALT at screening is >3x but <5x ULN, a re-test will be allowed. If ALT at re-test is <3x ULN and confirmed at another re-test, the patient will be eligible for participation). Chronic kidney disease as per NKF stages ≥4: eGFR ≤29 mL/min/1.73 m^2.
6. Clinically significant, abnormal vital sign data as judged by the investigator and verified with repeated testing.
7. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer, or longer if required by local regulations.
8. Prior treatment with any biologic drug targeting the immune system within 180 days of randomization.
9. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays.
10. Any conditions or significant medical problems which in the opinion of the investigator immune compromise the patient and/ or places the patient at unacceptable risk for immunomodulatory therapy, such as, but not limited to:
    a. Absolute neutrophil count (ANC) <1,500/µl
    b. Thrombocytopenia CTCAE v4.03 Grade 1: platelets <LLN (<100.0 x 10^9/L)
    c. Any active or recurrent bacterial, fungal (with exception of onychomycosis) or viral infection
    d. Presence of human immunodeficiency virus (HIV) infection, active hepatitis B or hepatitis C infections based on screening lab results
    e. Presence of active or latent tuberculosis (TB) or exposure risk established during screening such as, but not exclusively to:
       Close contact (e.g., share the same air space in a household or other enclosed environment for a prolonged period such as days or weeks, but not minutes or hours), with a person with active pulmonary TB disease within the last year, or

Evidence of TB infection (active or latent) determined by positive QuantiFERON test or positive purified protein derivative (PPD) test (≥5 mm induration) at screening or within 2 months prior to screening visit, according to national guidelines. If presence of TB infection is established then treatment for TB as per national guidelines must have been completed prior to randomization and definitive cure has been demonstrated. In the absence of national guidelines, the following has been demonstrated: TB has been treated adequately by antibiotics, definitive cure can be demonstrated and risk factors resulting in TB exposure and contracting have been removed.

11. Live vaccinations within 3 months prior to study drug dosing.
12. Current severe progressive or uncontrolled disease, which in the judgment of the clinical investigator renders the patient unsuitable for the trial.
13. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
14. Donation or loss of blood (amount depending on age and weight, 10-20% or more of volume, within 8 weeks prior to first dosing, or longer if required by local regulation.
15. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
16. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
17. Transcranial Doppler ultrasound in the past year or at screening in patients with an accessible transtemporal window, demonstrating velocity in middle or anterior cerebral or internal carotid artery ≥200 cm/sec.
18. Female of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of the investigational treatment and for up to three months after the last dose. Where basic contraception is sufficient for this study, abstinence should be encouraged in a pediatric population and if appropriate for sexually mature adolescents and young adult, barrier methods should be advised and/or hormonal methods can be prescribed after careful evaluation by a physician.

    Basic contraception methods include:

    - Total abstinence from heterosexual intercourse (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
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - 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.

Females within the age range of this study are considered not of child bearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

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

5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the following restrictions:

5.1 Contraception requirements

Please refer to exclusion criteria (Section 4) for details of contraception requirements for the study.

5.2 Prohibited treatment

Use of the treatments displayed in the table below are NOT allowed after the start of study treatment due to the concern for either increased potential immunosuppressant-related conditions or for potential impact on efficacy assessments . These are prohibited for the duration of the study until 90 days after discontinuation of study drug.

Table 5-1 Prohibited treatment

Medication	Action to be taken
Biologic drugs targeting the systemic immune system (e.g., TNFα blockers, anakinra, rituximab, abatacept, tocilizumab)	Discontinue study drug
Live vaccines (within 90 days of study drug dosing)	Discontinue study treatment; if live vaccines are given after screening but prior to study drug administration, the subject may be enrolled after 90 days have passed since vaccine administration if the subject continues to meet eligibility criteria upon rescreening
Systemic immune suppressive drugs, except for hydroxyurea maintained within a stable dosing regimen of >60 days prior screening	Discontinue study treatment if these medications are taken for more than 3 days. Maintain hydroxyurea at a stable dosing regimen throughout trial
Scheduled regular blood transfusion therapy	Discontinue from study

5.3 Dietary restrictions and smoking

There are no specific dietary restrictions.

5.4 Other restrictions

Not applicable.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the Site Operations Manual.

6.1.1 Investigational treatment and control drugs

The investigational drug, ACZ885 (canakinumab) 150 mg and matching placebo liquid vials will be prepared by Novartis and supplied to the Investigator as open labeled pack medication.

6.1.1.1 Bio-batch retention samples

Not applicable for this study.

6.1.2 Additional study treatment

No additional study treatment beyond investigational drug and control drug are included in this trial.

6.2 Treatment arms

Subjects will be assigned to one of the following two treatment arms in a ratio of 1:1. Study treatments are defined as:

During the blinded period:

- Monthly doses of 300 mg (4 mg/kg for patients ≤ 40 kg) canakinumab s.c.
- Monthly doses of placebo to match the administered dose of canakinumab s.c.

During the open label period:

- Monthly doses of 300 mg (4 mg/kg for patients ≤ 40 kg) canakinumab s.c.

6.3 Treatment assignment and randomization

Randomized treatment will be assigned to individual subjects by way of a randomization number. As stratification is planned for patients at treatment randomization according to presence or absence of concurrent hydroxyurea use, two randomization lists will be prepared: 5101-5190 for stratum 1 (presence of hydroxyurea use); 6101-6190 for stratum 2 (absence of hydroxyurea use). There is no minimal or maximal number to which either stratum is expected to reach. A longer randomization list is chosen here as the sample size may be increased at re-evaluation when the study approaches the first interim analysis (Section 11.7).

The randomization number is only used to identify which treatment the subjects have been randomized to receive. The Subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the SOM.

Subjects enrolled will use sequential subject numbering. There will be no replacement in this study, as a dropout rate of 20% is already taken into consideration in the sample size estimation.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office. 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 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 arms to randomization numbers in the specified ratio.

Follow the details outlined in the Site Operations Manual regarding the process and timing of randomization of subjects.

6.4 Treatment blinding

This is a subject and investigator-blinded study. Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below.

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

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study:

The unblinded site pharmacist or dedicated unblinded site personnel will assign the treatment according to the randomization list. Unblinded site personnel will only be involved in the treatment preparation for administration.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.7).

Sponsor staff

The following unblinded sponsor roles are required for this study:

Unblinded sample analyst(s) (PK blood)

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-1. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (e.g., biomarker expert) are allowed to access treatment assignment information for the purpose of conducting interim analyses.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Table 6-1 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis & dose escalation
Subjects/Patients	B	B	UI	B
Site staff	B	B	UI	B
Pharmacist and unblinded site staff	UI	UI	UI	UI
Drug Supply and Randomization Office	UI	UI	UI	UI
Statistician/statistical programmer/data analysts	B	B	UI	UI
All other sponsor staff not identified above	B	B	UI	UI

B Remains blinded

UI Allowed to be unblinded at individual patient level

6.5 Treating the subject

ACZ885 will be administered to the subject at the study site via subcutaneous injection, followed by a minimum, post-dose monitoring period of 15 minutes to monitor for evidence of hypersensitivity reaction to the IMP (e.g., altered vital signs, rash, headache).

See the Site Operations Manual for further details.

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

6.6 Permitted dose adjustments and interruptions of study treatment

Scheduled dosing of study drug may be delayed by up to 5 days if subjects present with conditions that require withholding of study drug, e.g., evidence for active infection (treated or untreated) or acute abdominal pain. Outside of this 5 day window, the dose will be considered missed. These changes must be recorded on the Dosage Administration Record CRF.

6.7 Emergency breaking of assigned treatment code

Emergency unblinding must only be undertaken when it is essential to treat the subject safely and efficaciously. 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. A complete set of emergency code break cards will be provided to the investigator site(s) and a complete set will be available at Novartis. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible to the investigator 24 hours per day in case of emergency. The investigator will receive a blinded code break card for each subject, with the details of study treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the

date, time, and reason for removing it and retain this information with the case report form documentation. **The unblinded treatment code must not be recorded on the CRF.** The investigator must also immediately inform the study monitor that the code has been broken.

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

- protocol number
- study drug name (if available)
- subject number.

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

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject and, if applicable, whether the subject can continue into the next trial phase.

6.8 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with ACZ885, as detailed in Section 8.7

6.9 Recommended treatment of adverse events

There is no treatment that can reverse the activity of ACZ885. Given that ACZ885 is an IgG1 isotype monoclonal antibody, plasmapheresis may be of value in removing ACZ885 from the body. Potential adverse events should therefore be treated symptomatically at the discretion of the Investigator. Medication used to treat AEs must be recorded on the concomitant medications/significant non-drug therapies eCRF.

6.10 Rescue medication

In the context of this study, rescue medications are defined as those medications used acutely to directly manage medical signs or symptoms related to the subject's underlying sickle cell disease. Patients may receive hydration and analgesics for chronic or episodic pain with recording of analgesic type and dosing information in daily diary. Patients are allowed to receive acute blood transfusions during the study; such intervention must be captured in the CRF.

6.11 Concomitant treatment

Subjects will be maintained on their pre-existing stable medical regimen for treatment of preexisting medical conditions, including sickle cell anemia. Common potential concomitant medications in this study population are anticipated to include analgesics and stable hydroxyurea therapy, defined as an hydroxyurea dosing regimen that remains fixed except for

any adjustments according to hematologic parameters or other standard of care clinical monitoring.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study must be recorded on the concomitant medications/significant non-drug therapies section of the CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. The study will complete when the last subject completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

7.2 Discontinuation of study treatment

Subjects may voluntarily discontinue from the study for any reason at any time. 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.

Any patient who discontinues the study early will complete the EOS visit, about 8 weeks after the last dosing visit.

If a subject discontinuation occurs for any reason, the investigator must make every effort to determine the primary reason for a subject's discontinuation from the study and record this information on the CRF.

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

Study treatment must be permanently discontinued under the following circumstances:

- Subject withdraws consent
- Pregnancy
- Severe allergic reaction or anaphylaxis following administration of the study drug
- Emergence of the following adverse events:
- Serious infections combined with neutropenia CTC grades ≥1 (ANC $<1.5 \times 10^9$/L)
- Confirmed diagnosis of active TB
- Onset of any malignancy
- Any of the following laboratory abnormalities:
    - Neutropenia CTCAE v4.03 Grades ≥3: neutrophils $<1.0 \times 10^9$/L
    - Thrombocytopenia CTCAE v4.03 Grade 3: platelets $<50.0 \times 10^9$/L

- Use of prohibited treatment as per Table 5-1.
- Any other protocol deviation that results in a significant risk to the patient's safety

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.

Subjects who discontinue study treatment should NOT automatically be considered withdrawn from the study.

For subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc.

Subjects who are withdrawn from the study before Week 24 for reasons other than safety or lack of efficacy will be replaced on a case-by-case basis.

7.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent from the study is defined as when a subject:

- Does not want to participate in the study anymore and
- Does not want any further visits or assessments and
- Does not want any further study related contacts and
- Does not allow analysis of already obtained biologic material.

In this situation, the investigator must make every effort (e.g., telephone, e-mail, letter) to determine the primary reason for the subject's decision to withdraw his/her consent and record this information.

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.

7.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, 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 cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study Stopping rules

All subjects will undergo regular monitoring at scheduled visits for safety and tolerability, including adverse events, throughout the duration of the study. If significant risk to the study subjects is identified, the study may be put on hold or terminated based on a full safety review.

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee of the early termination of this trial. In addition, the study will be paused if any of the following criteria are met, and no further dosing pending a full safety review:

- The observed proportion of patients having canakinumab-related serious adverse events such as infections, opportunistic infections, hypersensitivity, white blood cell (WBC) or platelet count decreases is 20% greater in canakinumab arm compared to placebo arm when enrollment is ≥10; when enrollment is below 10, at least 2 more patients with SAEs in the active arm than in the placebo arm.
- A series of similar, new unexpected serious adverse events considered related to canakinumab in more than 3 individuals on active therapy.

7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, patients must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient’s interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

Study Phase	Screening		Randomized Treatment							Open Label Treatment								Post-Treatment Follow-Up
Visit Name	Screening	Baseline	Randomized treatment							Open label treatment								EOS
Visit Numbers[1]	1	2	101		102	103	104	105	106[2]	201		202	203	204	205	206	207[2]	301[3]
Study Day(s)	-28 to -14	-14 to -1	1		29 ±3	57 ±3	85 ±3	113 ±3	141 ±3	169 ±3		197 ±3	225 ±3	253 ±3	281 ±3	309 ±3	337 ±3	393 ±7
Time (post-dose)	-	-	-1h[4]	0h	-	-	-	-	-	-1h	0h	-	-	-	-	-	-	-
Informed consent	X																	
Commercially Confidential Information																		
Inclusion / Exclusion criteria	S		S															
Concomitant therapies	X																	X
Medical history/current medical conditions	X																	
Demography	X																	
Alcohol Test and Drug Screen	S		S															
Tuberculosis status	S																	
Hepatitis screen	S																	
HIV screen	S																	
Pregnancy test	X		X		X	X	X	X	X	X		X	X	X	X	X	X	X
Body height			X															
Body weight	X		X		X	X	X	X	X	X		X	X	X	X	X	X	X
Physical examination	S		S		S	S	S	S	S	S		S	S	S	S	S	S	S
Body temperature	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure	X		X		X	X	X	X	X	X		X	X	X	X	X	X	X
Pulse rate	X		X		X	X	X	X	X	X		X	X	X	X	X	X	X
Study drug administration[10]				X	X	X	X	X	X		X	X	X	X	X	X		
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Study Phase	Screening		Randomized Treatment							Open Label Treatment								Post-Treatment Follow-Up
Visit Name	Screening	Baseline	Randomized treatment							Open label treatment								EOS
Visit Numbers[1]	1	2	101		102	103	104	105	106[2]	201		202	203	204	205	206	207[2]	301[3]
Study Day(s)	-28 to -14	-14 to -1	1		29 ±3	57 ±3	85 ±3	113 ±3	141 ±3	169 ±3		197 ±3	225 ±3	253 ±3	281 ±3	309 ±3	337 ±3	393 ±7
Time (post-dose)	-	-	-1h[4]	0h	-	-	-	-	-	-1h	0h	-	-	-	-	-	-	-
PK blood collection[5]			X		X		X		X	X								
Blood collection for IL-1β			X		X	X	X	X	X	X								
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Immunogenicity			X				X			X				X			X	
Clinical Chemistry	X		X		X	X	X	X	X	X		X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]
Hematology	X		X		X	X	X	X	X	X		X	X	X	X	X	X	X
Urinalysis			X		X	X	X	X	X	X		X	X	X	X	X	X	X
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Oxygen Saturation			X				X			X				X				
eDiary (Daily Pain VAS, Fatigue VAS, School/Work absence)	X[8]	X[8]	X															X
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Adverse events	X																	X
Serious adverse events	X																	X
Study completion information																		X

[1] Visit structure given for internal programming purpose only
[2] The end of each epoch is marked by the completion of the disposition CRF (X99) in the summary CRF section.
[3] For patients refusing the open label part or who stop the study early, the EOS will be conducted about 8 weeks after the last dosing.
[4] Baseline assessments can be performed on Day -1.
[5] The PK samples are taken pre-dose.
[6]
[7] Commercially Confidential Information

[8]

[9] Haptoglobin is not measured in these samples. Haptoglobin will only be measured at screening, randomized treatment period and V201.

[10] ACZ885 will be administered to the subject at the study site via subcutaneous injection, followed by a minimum, post-dose monitoring period of 15 minutes to monitor for evidence of hypersensitivity reaction to the IMP (e.g., altered vital signs, rash, headache).

[11] Commercially Confidential Information

S Source data only, not captured in the eCRF.

8.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If incapable of doing so, in cases where the subject's representative gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the subject.

Ensure subjects are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

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A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

8.3 Subject screening

Information on what data should be collected for screening failures is outlined in the Site Operations Manual.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the Site Operations Manual.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.4.1 Alcohol Test and Drug Screen

All subjects will be screened for substances of abuse. See the Site Operations Manual for details.

8.4.2 Tuberculosis status

Determination of TB status will be required before administration of study treatment and should be performed as defined by local guidelines. For those patients in whom the presence of TB infection is established, then the TB must be first adequately treated and definitive cure demonstrated.

Any significant findings will be recorded in the "Relevant medical history/Current medical conditions" section of the eCRF.

8.4.3 HIV screen

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot.

Appropriate counseling will be made available by the Investigator in the event of a positive finding. Notification of state and local authorities, as required by law, will be the responsibility of the Investigator.

Results will be available as source data and will not be recorded within the CRF.

8.4.4 Hepatitis screen

All subjects will be screened for Hepatitis B and C. See the Site Operations Manual for details.

8.5 Efficacy / Pharmacodynamics

Pharmacodynamic assessments are specified below, with the methods for assessment and recording specified in the Study Operations Manual. Assessments will be performed/samples collected at the timepoint(s) defined in the Assessment schedule.

In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

8.5.1 Clinical Outcome Assessments (COAs)

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8.5.1.2 eDiary

Pain diaries are commonly used to assess pain symptoms and response to treatment in children and adolescents with recurrent and chronic pain, with a recommended assessment time frame of at least 3 months (McGrath et al 2008). In SCA patients, daily diaries have been shown a more sensitive means of capturing reported pain frequency than through retrospective interviews (Porter et al 1998). Furthermore, electronic diaries have been shown in adolescents to have additional advantages over the paper format of accuracy as well as compliance in recording patient-reported outcomes (McGrath et al 2008). In this study, we will use e-diaries to record the following 5 daily outcomes:

a. Pain intensity. Most pain diaries use a simple visual analog scale (VAS) to record severity. Children with SCA have been shown in numerous studies to reliably self-report pain that is specifically attributable to sickle cell vaso-occlusion (Shapiro et al 1995; Dampier et al 2002a; Dampier et al 2004). In this study, pediatric and young adult patients will rate their daily sickle cell-associated pain intensity once each day in the evening using an 11-point numerical rating scale from 0 to 10 with higher ratings associated with more intense pain (0 = no pain, 10 = worst pain). Numerical rating scales are a valid and reliable assessment tool and have been recommended for assessment of pain intensity for both acute (Pagé et al 2012) and chronic pain (Ruskin et al 2014) in adolescents. In addition, patients noting pain above the level of 0 will be prompted to provide the approximate duration of their pain (<2hours, 2-6 hours, >6 hours).

b. Fatigue. Similar to pain intensity, a single item measure can be used for accurately capturing fatigue data in daily diaries, with convergent validity to validated, multiple-item measures of fatigue (Van Hooff et al 2007). In this study patients will be instructed to answer the question, "how fatigued do you currently feel?" using an 11-point numerical rating scale with higher rating associated with more severe fatigue (0 = not at all, 10 = extremely).

c. Interference with daily tasks. Study subjects will rate the extent that their sickle cell pain kept them from daily activities, such as seeing friends, doing chores, playing, sports, etc., using an 11-point numerical rating scale (0 = not at all, 10 = completely).

d. Medication use. Study subjects who respond, 'yes' for medication use are instructed to record the category of pain medication (acetaminophen/paracetamol, NSAID/COX-2 inhibitor, Narcotic, Other).

e. Absence from school and/or work. Study subjects will answer whether they have missed any school or job time. (Yes, missed due to SCA; Yes, missed due to other reasons; No, did not miss; No, but I am not a student/have no job; No school/work today (weekend, break, holiday, etc.).

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment Schedule (Section 8.1) detailing when each assessment is to be performed.

8.6.1 Blood pressure

Blood pressure (BP) will be measured

8.6.2 Body height

Height will be measured.

8.6.3 Body temperature

Body temperature will be measured.

8.6.4 Body weight

- Body weight will be measured
- Body mass index (BMI) will be calculated as (body weight (kg) / [height (m)]^2)

8.6.5 Clinical Chemistry

Sodium, potassium, magnesium, protein, creatinine, BUN/urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, direct and indirect bilirubin, bicarbonate/HCO_3, LDH, γ-GT AST, ALT, amylase, lipase, CK, glucose, total cholesterol, triglycerides, LDL, HDL, hs-CRP, haptoglobin.

8.6.6 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differentials and reticulocyte count will be measured.

8.6.7 Immunogenicity

To assess potential immunogenicity, serum samples for detection of anti-canakinumab antibodies will be collected during the study (see Assessment Schedule).

The instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing, and shipment will be followed.

In the case of an anaphylactic reaction occurring after injection, a sample will be taken at the time of the event and 8 weeks later. An immunogenicity positive subject at the end of the study will be followed up for three months.

Immunogenicity analytical method

An ELISA-based method will be used for the detection of potential anti-canakinumab antibody formation. The detailed method description to assess immunogenicity will be described alongside the bioanalytical raw data of the study in the respective Bioanalytical Data Report (BDR).

8.6.8 Pulse rate

Pulse rate will be measured

8.6.9 Urinalysis

Dipstick measurements for specific gravity, albumin, protein, glucose and blood will be performed. Microscopy, WBC, RBC and sediments will also be assessed in case of an abnormal dipstick test.

8.6.10 Pregnancy test

All pre-menopausal women who are not surgically sterile will have pregnancy testing. See the Assessment Schedule Section 8.1, for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements*. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

*If additional pregnancy testing is needed per local requirements, those additional results will be kept as source documentation only.

8.6.11 Physical examination

See Site Operations Manual for details.

8.7 Pharmacokinetics

PK samples will be collected at the time points defined in the Assessment schedule, Section 8.1. The instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing and shipment will be followed. See Section 8.9 regarding the potential use of residual samples.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

Pharmacokinetic (PK) samples will be obtained and evaluated in all subjects at all dose levels.

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For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

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zero in summary statistics. The geometric mean will not be reported if the dataset includes zero values.

8.8 Other assessments

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8.9 Use of residual biological samples

Residual blood and urine samples may be used for another protocol specified endpoint.

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9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign including abnormal laboratory findings, symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.5 for an overview of the reporting requirements.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively.

Pre-existing medical conditions/diseases (i.e., Medical History(ies)) are considered AEs if they worsen after providing written informed consent.

Adverse events must be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the severity grade
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. its relationship to study treatment
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. whether it constitutes an SAE (see Section 9.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- investigational treatment dosage increased/reduced
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)

6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). Once an adverse event is detected, it must 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 investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

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

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of an 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 (see Annex IV, ICH-E2D Guideline).

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. 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 (see Annex IV, ICH-E2D Guideline).

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

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Drug Safety & Epidemiology (DS&E) as per Section 9.2.2.

9.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis **within 24 hours of learning of its occurrence** as described below. Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Note: SAEs reported by subjects deemed to be screen failures must be reported to Novartis as outlined here with appropriate information also captured in the CRFs as specified in the Site Operations Manual.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

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 study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment 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.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. Note: **SAEs must be reported to Novartis within 24 hours** of the investigator learning of its occurrence/receiving follow-up information.

9.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 15-1-Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Table 15-1-Appendix 1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 15-2-Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and γGT) to confirm elevation within 48-72 hours.

  These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 7.2 (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
  - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and γ-GT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
  - Exclusion of underlying liver disease, as specified in Table 15-3.
  - Imaging such as abdominal US, CT or MRI, as appropriate
  - Obtaining a history of exposure to environmental chemical agents.
  - Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

9.4 Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Section 16-Appendix 2.

9.5 Reporting Medication errors including misuse/abuse

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

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

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

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Novartis Drug Safety and Epidemiology department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Drug Safety and Epidemiology. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Summary of reporting requirements for medication errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with an SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.6 Pregnancy reporting

To ensure patient safety, each pregnancy in a subject on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatments.

Any SAE experienced during pregnancy and unrelated to the pregnancy must be reported on an SAE Report Form.

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.7 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the

protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the 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 on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (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 CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.2 Data collection

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

Data not requiring a separate written record will be defined in the Site Operations Manual and Assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

10.3 Database management and quality control

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

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

Diary data will be entered into an electronic diary by the subject. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis (or a 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.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the COAR Analytics NIBR Franchise Head and the relevant NIBR TA Head.

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10.4 Data Monitoring Committee

Not required.

10.5 Adjudication Committee

Infection Adjudication Committee

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

The mission of the canakinumab IAC is to independently and blinding review, evaluate and categorize new reports of pre-defined infections as they become available during the conduct of this trial.

The members, detailed mission and procedures of the IAC are detailed in the IAC charter which is available upon request.

Malignancy Adjudication Committee

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

The mission of the MAC is to independently and blinding review, evaluate and categorize reports of malignancy events across all potential indications and therapeutic areas in the canakinumab development program.

The members, detailed mission and procedures of the MAC are detailed in the MAC charter which is available upon request.

11 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation. The key safety and efficacy endpoints will also be reported for pediatric (<18 years old) and adult (>=18 years old) cohorts separately per internal SOP requirement. Details will be explained in statistical analysis plan document.

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The primary PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data. For example, patients missing more than two consecutive doses or more during the blinded treatment period will be excluded from the primary PD analysis set. The secondary PD analysis set will include all subjects with available PD data.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group. Subject demographics will include age, gender, race, ethnicity, country, height, weight and BMI. Baseline disease characteristics include but are not limited to: baseline average daily pain VAS, baseline hs-CRP, the number of VOPE in the previous year.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

11.3 Treatments

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

11.4 Analysis of the primary variable(s)

The primary aim of this study is to assess if inhibition of IL-1β by canakinumab will reduce average daily pain in pediatric and young adult patients with sickle cell anemia. Statistical analysis plan for this primary endpoint will be described below in details.

11.4.1 Variable(s)

A numerical pain VAS score between 0 and 10 will be recorded by each patient once daily. An average daily pain VAS will be calculated for every 4 weeks and the reduction from baseline of the 4-week average daily pain VAS will be the primary variable for this study.

11.4.2 Statistical model, hypothesis, and method of analysis

The post-baseline average daily pain VAS will be calculated for each dose from the start of the dose till the day before the next dose, i.e. in an averagely 4-week interval (e.g., Week 0-4, Week 4-8, etc. depending on the actual dosing days). The baseline average pain VAS will be calculated as the average of daily pain scores from screening up to pre-dosing over a period of at least 7 days. Reduction from baseline in the average daily pain VAS, i.e., baseline minus post-baseline, will be analyzed using a Bayesian model for repeated measures using Proc MCMC in SAS (Chen 2011). The model will include baseline average daily pain score as a continuous covariate; treatment group, time and hydroxyurea use history (Yes/No) as fixed factors. Interactions of time by treatment group and time by baseline covariates will also be included in the model. Non-informative priors will be used for the fixed effects and weakly informative prior, for the covariance. Unstructured covariance structure will be used and other covariance structure will be investigated if there is convergence problem. Interaction of hydroxyurea use and treatment group will be explored via visualizations; if substantial interaction is suspected it will be further explored by including this interaction term in the whole model.

A comparison of canakinumab 300 mg s.c. versus placebo for the period of Week 8-12 is of primary interest. Data up to Week 12 will be included in the primary model. Bayesian posterior probabilities will be used to assess the following PoC criteria as a guidance for decision making (Fisch et al 2015):

Prob (the reduction of average pain score over the period of Week 8-12 in canakinumab is greater than Placebo) > 90%, and

Prob (the reduction of average pain score over the period of Week 8-12 in canakinumab is greater than Placebo by 1) > 50%.

The target difference of 1 is chosen based on the literature search on the Minimally Clinical Important Difference (MCID) in pain studies (see Section 11.7).

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Data up to Week 24 will also be analyzed with the same model specifications when there are at least about 50% completers at Week 24 and also upon the study completion. Pain data in the open label period when available will also be summarized, visualized and explored in

appropriate statistical models, to evaluate the maintenance of the efficacy in patients randomized to canakinumab group and/or improvements in patients randomized in placebo group.

11.4.3 Handling of missing values/censoring/discontinuations

For the primary analysis, data for those patients who have received acute blood transfusion(s) during the study will be truncated up to the first occurrence of acute blood transfusion, i.e. data since the first blood transfusion will be considered as missing. Assuming the occurrence of acute blood transfusion being random to this patient population, such missing data are considered Missing at Random (MAR). As a supportive analysis, the complete data will be analyzed as if the patients did not receive any blood transfusion (Section 11.4.5).

Early discontinuations not due to lack of efficacy support the assumption of Missing at Random (MAR). In such scenarios MMRM remains valid. In the primary analysis for the blinded treatment period, if there were any patients who discontinued early due to lack of efficacy, LOCF (last observation carried forward) approach will be applied as a sensitivity analysis to deal with such missing data.

11.4.4 Sensitivity analyses

An Intention-To-Treat (ITT) analysis will also be explored as a sensitivity analysis to include all patients who received at least one study drug treatment (the second PD analysis set), if there are patients excluded in the primary PD analysis set, for example those who have missed two consecutive dosing or more.

11.4.5 Supportive analyses

As a supportive analysis, all collected data in the double-blinded period will be analyzed in the same way as described in Section 11.4.2, without truncation of data due to acute blood transfusions. This is to explore the possible impact of such rescue therapy to the treatment effect.

Non-convergence of the primary analysis may occur when there is a great amount of truncated data due to acute blood transfusion. In that scenario the evaluation of efficacy may focus on the analysis of the rate of acute blood transfusion (Section 11.5.4).

11.5 Analysis of secondary variable(s)

For the double-blinded period, the main analysis on secondary efficacy data, including inflammation and hemolysis biomarkers, absence from school/work will also be based on truncated data up to the time of the first acute blood transfusion where applicable. Complete data will also be summarized and visualized.

11.5.1 Efficacy / Pharmacodynamics

To determine the duration of effects of canakinumab versus placebo on daily pain, the average daily pain VAS data after Week 12 will be analyzed, as explained in Section 11.4.2. The daily pain data will also be explored using visualizations.

11.5.2 Inflammation and hemolysis biomarkers at Week 12

The inflammation biomarkers, including hs-CRP, WBC count, absolute count of blood neutrophils and absolute count of blood monocytes, will be summarized and visualized by treatment group and visit/time. For each of the inflammation biomarkers, change from baseline taken from log transformed values will be analyzed using an MMRM with the log baseline value as continuous covariate, treatment group, time, hydroxyurea use history (Yes/No) and race as factors. Unstructured covariance structure will be used.

The hemolysis biomarkers, including hemoglobin concentration, reticulocyte count, haptoglobin, lactate dehydrogenase, total bilirubin, direct and indirect bilirubin and oxygen percent saturation (SaO2), will also be summarized and visualized by treatment group and visit/time. The same MMRM approach as for inflammation biomarkers will also be applied for each individual hemolysis biomarker with log transformation.

For each of the biomarkers, the difference between canakinumab and placebo groups at Week 12 will be presented in terms of ratio of geometric mean because of the log transformation.

11.5.3 Absence from school/work

The number of SCA-related days absent from school or work will be derived from eDairy records. The data will be summarized and visualized by treatment group and visit/time. A negative binomial Generalized Linear Model (GLM) will be fitted for the total number of SCA-related days absent from school/work up to Week 24 visit, with treatment group as the factor. The difference between canakinumab and placebo groups will be estimated.

11.5.4 Incidence of acute blood transfusion

The occurrence of acute blood transfusions will be summarized as the proportion of patients who receive at least one acute blood transfusion and the event rate of acute blood transfusions per patient during double-blinded period and open-label period separately.

The proportion of patients who receive at least one acute blood transfusion during the double-blinded period will be analyzed in a binomial Bayesian model with non-informative prior for both groups (neutral prior Beta(1/3, 1/3), (Kerman 2011) and the posterior probability of the difference of the two proportions (placebo – ACZ885) will be presented.

If the data allows, the recurrent event analysis (at least one patient receiving more than one acute blood transfusion), the time to recurrent incidence of acute blood transfusions during the double-blinded period will be analyzed via the Andersen-Gill model (Andersen & Gill 1982), with treatment and hydroxyurea use as independent variables and time to last blood transfusion before study treatment (if available) as a continuous covariate.

The incidence of acute blood transfusions will also be included in the visualizations of all efficacy endpoints where applicable.

11.5.5 Safety

Vital signs

All vital signs data will be listed by treatment group, subject and visit/time, and where ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data Commercially Confidential Information will be listed by treatment group, subject, and visit/time, and where normal ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

The proportion of patients receiving any rescue medication/therapy post baseline will be summarized by group and study period.

Immunogenicity

All immunogenicity results will be listed by treatment group, subject and visit/time.

11.5.6 Pharmacokinetics

Canakinumab plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ (lower limit of quantification) which will be reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. The impact of acute blood transfusions on PK data may be explored.

11.5.7 Pharmacokinetic / pharmacodynamic interactions

Not applicable.

11.5.8 Other assessments

Not applicable.

11.6 Analysis of exploratory variables

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11.7 Sample size calculation

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11.8 Power for analysis of key secondary variables

Not applicable.

11.9 Interim analyses

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12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. 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 Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an

investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an 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 and health authorities, where required, it cannot be implemented.

13.1 Protocol Amendments

Any change 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 prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

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, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

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15 Appendix 1: Liver Event Definitions and Follow-up Requirements

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	• ALT > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT elevation with coagulopathy	• ALT > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT elevation accompanied by symptoms	• ALT > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT elevation	• ALT > 8 × ULN • 5 x ULN < ALT ≤ 8 x ULN • 3 x ULN < ALT ≤ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) • Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case ALT elevation with coagulopathy ALT elevation accompanied by symptoms Isolated ALT elevation > 8 × ULN Jaundice	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance
Isolated ALT elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance
Isolated ALT elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance

Criteria	Actions required
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM 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, γ-GT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16 Appendix 2: Specific Renal Alert Criteria and Actions

Table 16-1 Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 16-2 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Monitor subject regularly (frequency at investigator's discretion) until:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

* Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.