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Novartis Research and Development

ACZ885/Canakinumab

Clinical Trial Protocol CACZ885G1302 / NCT04717635

An open-label, single-arm, active-treatment study to evaluate efficacy and safety of canakinumab (ACZ885) administered for at least 48 weeks in Japanese patients with Adult Onset Still's Disease (AOSD)

Document type:	Amended Clinical Trial Protocol
EUDRACT number:	2021-003706-50
Version number:	03 (Clean)
Clinical Trial Phase:	III
Release date:	19-May-2023 (content final)

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List of abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse Event
AESI	AEs of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AOSD	Adult-onset Still's disease
ASD	Adult still's disease
AST	Aspartate Aminotransferase
BCG	Bacillus Calmette-Guerin
BDR	Bioanalytical Data Report
BP	blood pressure
BSL	Baseline
BUN	Blood Urea Nitrogen
CK	Creatinine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CTT	Clinical Trial Team
CV	coefficient of variation
DAS	Disease Activity Score
DIC	Disseminated intravascular coagulation
DIN	Drug Inducted Nephrotoxicity
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	end of study
CCI	[redacted]
eSource	Electronic Source
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
h	Hour
HAQ	Health Assessment Questionnaire
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus

HIV	Human immunodeficiency virus
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
JIA	Juvenile Idiopathic Arthritis
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
MAS	Macrophage Activation Syndrome
MCS	Mental Component Summary
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MRI	Magnetic resonance imaging
mSv	milisievert
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
PCR	Protein-creatinine ratio
PCS	Physical Component Summary
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PPD	Purified protein derivative
PRO	Patient Reported Outcomes
PSD	Premature Subject Discontinuation
PT	prothrombin time
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RA	Rheumatoid arthritis
RBC	red blood cell(s)
RDC	Remote Data Capture
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	standard deviation
CCI	[redacted]
SJIA	Systemic Juvenile Idiopathic Arthritis

SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
ULN	upper limit of normal
UTI	Urinary Tract Infection
VAS	Visual Analog Scale
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the participant about the status of a participant's health condition without amendment or interpretation of the participant's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis

Personal data	Participant information collected by the Investigator that is coded and transferred to Novartisfor the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Remote	Describes any trial activities performed at a location that is not the investigative site.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation.

Amendment 3 (19-May-2023)

Amendment rationale

The main purpose of this amendment is the following:

To add timing and target patient number for interim analyses CCI [redacted]

To update description for MAS adjudication committee based on the recent canakinumab program updates.

To add oral JAK inhibitor in prohibited medication

To update according to latest protocol template at Novartis (version 5.0)

Changes to the protocol

Other minor corrections/clarifications were made where applicable. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

Amendment 2 (19-Jul-2021)

Amendment rationale

The main purpose of this amendment is following.

Clarified the visits to perform ultrasound sonography for liver and spleen since the previous description of systemic feature score assessment was unclear.

Canakinumab is a monoclonal antibody with no effects in renal function, with a well characterized preclinical and clinical safety profile, and with no known potential to cause drug-induced nephrotoxicity, for this reason there is no need for special renal safety monitoring.

CCI

Updates referring to version 4.0 of One CTP template.

Changes to the protocol

CCI

Other minor corrections/clarifications were made where applicable. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

Amendment 1 (29-Oct-2020)

Amendment rationale

The main purpose of this amendment is to revise some minor changes and typographical errors.

Changes to the protocol

CCI

Other minor corrections/clarifications were made where applicable. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

Protocol summary

Protocol number	CACZ885G1302
Full Title	An open-label, single-arm, active-treatment study to evaluate efficacy and safety of canakinumab (ACZ885) administered for at least 48 weeks in Japanese patients with Adult Onset Still's Disease (AOSD)
Brief title	Study of efficacy and safety of canakinumab in Japanese patients with Adult Onset Still's Disease (AOSD)
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess efficacy and safety of canakinumab administered for at least 48 weeks in Japanese AOSD participants with an inadequate response to corticosteroid therapy. Results of this study will be used for an approval application for the additional indication of ASD.
Primary Objective(s)	The primary objective of this study is to evaluate the efficacy of canakinumab with respect to the adapted ACR 30 response after 8 weeks treatment. The primary clinical question of interest is: What is the benefit of Canakinumab in achieving clinical improvement for Japanese AOSD participants without increased use of corticosteroids regardless of study treatment discontinuations for any reason?
Secondary Objectives	• To evaluate ability of canakinumab to taper corticosteroids based on success criteria starting from Week 8 to Week 28 • To evaluate the efficacy of canakinumab with respect to the adapted ACR 30/50/70/90/100 response over time • To evaluate the efficacy of canakinumab on the systemic feature score over time • To evaluate the efficacy of canakinumab with respect to the components of adapted ACR criteria over time • To evaluate ability of canakinumab to taper corticosteroids over time • To evaluate the efficacy of canakinumab on rash over time • To evaluate the efficacy of canakinumab on DAS28-CRP • To assess the safety and tolerability of canakinumab • To evaluate the pharmacokinetics (PK) / pharmacodynamic (PD) of canakinumab • To assess the immunogenicity of canakinumab
Study design	This is an open-label, single-arm active treatment study to evaluate efficacy, safety, tolerability and PK/PD of canakinumab 4 mg/kg (maximum of 300 mg) every four weeks administered subcutaneously for at least 48 weeks in Japanese participants with AOSD. This study will continue until canakinumab is approved and commercially available for ASD in Japan or Novartis terminates the study.
Rationale	Study G1302 is an open-label, single-arm study in Japanese AOSD patients to evaluate the efficacy and safety of canakinumab 4 mg/kg (maximum 300 mg) subcutaneously administered every 4 weeks. Conducting a large-scale confirmatory trial is not feasible because the number of AOSD patients who can be enrolled in this study is limited. Regarding the rationale for an open-label study, placebo administration to AOSD participants who do not respond to corticosteroids has a safety risk of worsening the underlying disease leading to macrophage activation syndrome (MAS), a serious complication that can be fatal. Since tocilizumab is available as an approved treatment option in Japan, conducting a placebo-controlled study for AOSD participants who do not respond to corticosteroids would not be enrolled. In addition, SOC control arm of tocilizumab is not feasible, since controlled trial with tocilizumab failed and G1302 study allows participants previously treated with tocilizumab who have discontinued treatment due to safety or efficacy issues to enter study.

	To compare the efficacy for Japanese AOSD and previously-treated SJIA participants, assessment time points for primary and key secondary endpoint are consistent with those evaluated in the SJIA study. Adapted ACR 30 will be assessed at Week 8 as primary endpoint. If improvements in disease activity are observed after Week 8, tapering of corticosteroid dose will be started, and the proportion of participants who have successfully reduced steroid dose at Week 28 will be assessed as a key secondary endpoint.
Study population	The study population will consist of male/female participants with a confirmed diagnosis of AOSD (≥16 years of age) who had inadequate response to corticosteroid therapy
Key Inclusion criteria	● Signed informed consent must be obtained prior to participation in the study. ● Japanese male/female participants aged ≥ 16 years ● Confirmed diagnosis of AOSD as per Yamaguchi classification criteria (Yamaguchi M, 1992) with an onset of disease ≥ 16 years of age. ● Active disease at the time of baseline defined as follows - Fever (body temperature > 38°C) due to AOSD for at least 1 day within 1 week before baseline - At least 2 active joints (tender or swollen) - CRP ≥ 10 mg/L ● Participants who have history of inadequate response to more than 2 weeks of corticosteroids equivalent to at least 0.4 mg/kg/day of prednisolone
Key Exclusion criteria	● History/evidence of active MAS or disseminated intravascular coagulation (DIC) within 6 months of enrollment. ● Underlying metabolic, renal, hepatic, infectious or gastrointestinal conditions which in the opinion of the investigator compromises the participant and/ or places the participant at unacceptable risk for participation in an immunomodulatory therapy. ● Positive TB screening test (chest X-ray and Quantiferon TB test) at screening visit or within 4 weeks prior to the screening visit. ● Active or recurrent bacterial, fungal or viral infection at the time of enrollment, including participants with evidence of Human Immunodeficiency Virus (HIV) infection, Hepatitis B and Hepatitis C infection. ● History of malignancy of any organ system, treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases, with the exception of localized excised non-melanomatous skin lesions.
Study treatment	Canakinumab 4 mg/kg (maximum of 300 mg) administered subcutaneously every 4 weeks at the study site throughout the study.
Treatment of interest	Canakinumab 4 mg/kg s.c (maximum of 300 mg) with stable dose of corticosteroids. Further details about the investigational treatment are provided in Section 6
Efficacy assessments	● Adapted ACR criteria ● Physicians global assessment of disease activity (VAS) ● Participants assessment of disease activity (Participant's overall well-being /Pain) on a 0-100 mm (VAS) ● Functional ability assessed using Health Assessment Questionnaire (HAQ) ● Number of active joints (tender or swollen joints) ● C-reactive protein (CRP) ● Fever assessment ● Steroid tapering ● Rash assessment ● Systemic feature score ● DAS28-CRP
Key safety assessments	● Adverse events ● Physical examination ● Vital signs ● Laboratory evaluation (hematology, chemistry, urinalysis) ● Electrocardiogram ● Pregnancy test/assessment of fertility ● Local tolerability

Other assessments	● Clinical Outcome Assessments (COAs) CCI - Trial Feedback ● Pharmacokinetics(PK) ● Immunogenicity(IG) ● Pharmacodynamic(PD) CCI
Data analysis	The primary analysis set is the full analysis set (FAS) which comprises all participants who received at least one dose of study treatment. The primary estimand is the response to treatment according to the adapted ACR 30 criteria at Week 8 excluding the effect of corticosteroid increase and/or intravenous administration of corticosteroid. The primary objective will be achieved if the null hypothesis is rejected at the 2.5 % one-sided level of significance. H_0:$p_{ACZ} \leq 0.40$ vs. H_A:$p_{ACZ} > 0.40$, with p_{ACZ} being the proportion of participants who achieved adapted ACR 30 at Week 8. Frequency tables with the number and percentage of participants who achieved adapted ACR 30 response together with a 95% confidence interval will be provided. A binomial test using the normal approximation will be performed. The secondary estimand is the effect of canakinumab on corticosteroids tapering at Week 28. Frequency tables with the number and percentage of participants who were able to taper corticosteroids successfully at Week 28 will be provided for the FAS.
Key words	Canakinumab, AOSD, IL-1β, Japanese participants

1 Introduction

1.1 Background

Adult-onset Still's disease (AOSD) is a concept of disease proposed by Bywaters (Bywaters 1971), who described an illness starting in adulthood (≥16 years of age) with symptoms similar to those of systemic juvenile idiopathic arthritis (SJIA). The pathogenesis of AOSD is unknown, but activation of innate immune cells, such as macrophages and dendritic cells, and overproduction of inflammatory cytokines, such as interleukin (IL)-1, IL-6, and IL-18, are thought to play key roles in the pathogenesis. The major clinical symptoms of AOSD are the triad of fever, joint symptoms, and rash. Fever often manifests as intermittent fever with a peak between evening to night. Joint symptoms occur in ≥80% of patients and often manifest as polyarthritis mainly in hands, feet, knees, and small joints of fingers. Rash is typically a salmon-colored flat rash that occurs along with onset of fever but is transient and disappears at normal body temperature. Urticaria and pruritis with dermographism have also been reported as cutanous manifestations in AOSD patients but are rather atypical. Characteristic laboratory findings are increased leukocytes and neutrophils, elevated CRP, and significant increases in serum ferritin. It is known that an increase in disease activity of AOSD or viral infection triggers development of a complication called macrophage activation syndrome (MAS), which may lead to a serious or fatal outcome (Gerfaud-Valentin et al 2014, Feist et al 2018). AOSD and SJIA share many common features including similar pathophysiology, clinical signs and symptoms at onset, laboratory findings and important complications. Therefore, they are considered similar conditions within the same disease continuum (Junge et al 2017, Mimura et al 2018, Martini et al 2019, Feist et al 2018, Tada et al 2019).

In Japan, both pediatric-onset (<16 years of age) SJIA that has been continued into adulthood (≥16 years of age) and AOSD which develops at ≥16 years of age is referred to as adult Still's disease (ASD). ASD is a concept of disease unique to Japan and a rare disease designated as an intractable disease. There are an estimated 4,760 Japanese ASD patients, with an estimated prevalence of 3.7 per 100,000 persons, according to a nationwide epidemiology survey conducted by the Research Study Group for Designated Autoimmune Diseases in 2011. Among ASD cases, SJIA prolonged to adulthood accounts for 12%, and AOSD accounts for 88% (Japan Intractable Diseases Information Center 2020). Canakinumab is approved for the SJIA indication in Japan and can be used for the treatment of SJIA prolonged to adulthood. However, since canakinumab is not approved for the treatment of AOSD in Japan, the drug cannot be used for AOSD patients.

Anti-inflammatory drugs including corticosteroids are mainly used empirically for the treatment of AOSD, similar to other autoinflammatory diseases in both Japan and foreign countries. In Japan, clinical practice guidelines for adult Still's disease were issued by the Research Study Group on Autoimmune Diseases in 2017 and strongly recommends systemic corticosteroids to improve clinical symptoms and pathological conditions of AOSD (Research Study Group on Autoimmune 2017). The dose of a corticosteroid is adjusted depending on severity of organ disorder and general condition, and steroid pulse therapy is used in patients with severe organ disorder. Because of concerns about adverse drug reactions with long-term use of corticosteroids, such as infection and corticosteroid-induced osteoporosis, the dose is gradually reduced as clinical symptoms and laboratory findings improve, but relapse

may occur during dose reduction of corticosteroids. Addition of DMARDs, such as the immunosuppressant methotrexate (MTX) and use of biologics are considered for AOSD patients who experience repeated relapses during dose reduction or are refractory to corticosteroids. In Japan, tocilizumab became available in May-2019 for the treatment of adult Still's disease in patients who did not respond to conventional therapy and is the only biologic at this point that is approved for the ASD indication. As described above, long-term use of high-dose corticosteroids, the current first-line therapy in the treatment of AOSD, is difficult because of the concern about adverse drug reactions. Some AOSD patients are refractory to tocilizumab, the only biologic that is currently approved for the ASD indication, and patients suffer burdens associated with the interval and method of tocilizumab administration. Thus, there is an unmet medical need for a new treatment option to solve these problems.

Canakinumab is a recombinant human immunoglobulin G1 monoclonal antibody directed against human IL-1β that neutralizes the activity of IL-1β by binding to it and thereby inhibiting its binding to the receptor.

In Europe, canakinumab was approved for the SJIA indication in August-2013. Then, the indication was expanded to include AOSD in August-2016 without conducting any additional clinical study in patients with SJIA or AOSD. An approval application for the additional indication of AOSD was filed based on the following: literature review results showing that SJIA and AOSD are similar diseases, IL-1β inhibitors are safe and effective in AOSD patients, a pooled analysis of SJIA studies showing canakinumab is effective and safe across age groups, and modeling and simulation results supporting the extrapolation of study data from children with SJIA to adults with AOSD.

In the United States, canakinumab was approved for the SJIA indication in May-2013. To expand the indication to Still's disease including SJIA as well as AOSD, an application for partial change in approval of a biologic was submitted to Food and Drug Administration (FDA) in December-2019 and approved in June-2020.

AOSD and SJIA are similar diseases sharing common clinical symptoms, laboratory features, and response to IL-1β inhibitors. Data from the pooled analysis of SJIA data demonstrate similar efficacy and safety profiles of canakinumab throughout the age groups, and the results of G2301 study and G1301 study show similar pharmacokinetics (PK) of canakinumab in Japanese and non-Japanese SJIA patients. Additionally, an investigator-initiated trial in non-Japanese AOSD patients (GDE01T study) consistently showed greater improvement in efficacy endpoints, such as improvement in DAS28-ESR and American College of Rheumatology (ACR) response rate, in the canakinumab group compared with the placebo group, although statistical significance was not achieved due to early termination of the study for lack of enrollment (see investigator brochure for details). Taken together, canakinumab was considered effective for AOSD as well as for SJIA.

Although canakinumab is approved for use in SJIA patients in Japan, there is no experience in use of canakinumab in Japanese AOSD patients so far. This study is planned to evaluate the efficacy and safety profile of canakinumab in Japanese AOSD patients.

1.2 Purpose

The purpose of this study is to assess efficacy and safety of canakinumab administered for at least 48 weeks in Japanese participants with AOSD who had an inadequate response to corticosteroid therapy. Results of this study will be used for an approval application for the additional indication of ASD.

The study allows participants to continue canakinumab treatment until it is approved and commercially available for the indication of ASD in Japan or Novartis terminates the study.

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● To evaluate the efficacy of canakinumab with respect to the adapted ACR 30 response after 8 weeks treatment	● Proportion of participants who achieve adapted ACR 30 response at Week 8
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● To evaluate ability of canakinumab to taper corticosteroids based on success criteria starting from Week 8 to Week 28	● Proportion of participants who are able to taper corticosteroids based on success criteria at Week 28.
● To evaluate the efficacy of canakinumab with respect to the adapted ACR 30/50/70/90/100 response over time	● Proportion of participants who achieved adapted ACR 30/50/70/90/100 response criteria at Day 15 and all subsequent visits.
● To evaluate the efficacy of canakinumab on the systemic feature score over time	● Change from baseline in Systemic Feature Score (total score and each components) at Day 15 and all subsequent visits.
● To evaluate the efficacy of canakinumab with respect to the components of adapted ACR criteria over time	● Change from baseline in each component of adapted ACR at Day 15 and all subsequent visits
● To evaluate ability of canakinumab to taper corticosteroids dose over time after Week 8	● Change from baseline of corticosteroid dose at all visits after Week 8.
● To evaluate the efficacy of canakinumab on rash over time	● Presence of rash (typical/atypical) at all visits during study.
● To evaluate the efficacy of canakinumab on DAS28-CRP	● Change from baseline in DAS28-CRP at Day 15 and all subsequent visits.
● To assess the safety and tolerability of canakinumab	● Incidence and severity of Treatment Emergent AEs. Proportion of participants up to end of study with: - Adverse events - Serious adverse events - AEs related to study drug - AEs leading to discontinuation ● Means and mean change over time of: - Vital sign parameters - Laboratory parameters
● To evaluate the pharmacokinetics (PK) / pharmacodynamic (PD) of canakinumab	● Canakinumab concentrations over time ● Total IL-1β (sum of IL-1β free and bound to canakinumab) level s over time
● To assess the immunogenicity of canakinumab	● Anti-canakinumab antibody identification and titer at BSL, Week 24, Week 48 and every 24 weeks until EOS.

Objective(s)	Endpoint(s)
Exploratory objective(s)	Endpoint(s) for exploratory objective(s)
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2.1 Primary estimands

The primary clinical question of interest is: What is the benefit of Canakinumab in achieving clinical improvement for Japanese AOSD participants without increased use of corticosteroids regardless of study treatment discontinuations for any reason?

The justification for the primary estimand is that it will capture the actual effect of canakinumab in the condition that participants use stable dose of corticosteroids. Further details can be found in Section 12.

The primary estimand is described by the following attributes:

1. Population: Japanese AOSD participants. Further details about the population are provided in Section 5.
2. Endpoint: Adapted ACR 30 response at Week 8
3. Treatment of interest: canakinumab 4 mg/kg s.c (maximum of 300 mg) with stable dose of corticosteroids.

Handling of remaining intercurrent events:

1. Systemic corticosteroid dose increase and/or iv corticosteroid use before Week 8 for any reason: consider as non-response (Composite variable strategy)
2. Study treatment discontinuation for any reason: ignore (if adapted ACR 30 at Week 8 is available, it will be included in the analysis) (Treatment policy strategy)

The summary measure: Proportion of participants who achieve adapted ACR 30 at Week 8

2.2 Secondary estimands

The secondary clinical question of interest is: What is the effect of Canakinumab on oral corticosteroids tapering in Japanese AOSD participants after Week 8 up to Week 28?

The justification for the secondary estimand is that it will capture the ability of canakinumab on corticosteroid tapering based on the success criteria starting from Week 8 up to Week 28 after canakinumab administration.

The secondary estimand is described by the following attributes:

1. Population: Japanese AOSD participants who use systemic corticosteroid at baseline and are administered canakinumab at Week 8. Further details about the population are provided in Section 5.
2. Endpoint: Successful oral corticosteroids tapering at Week 28. Participants will be considered as being able to taper oral corticosteroid according to pre-defined criteria depending on baseline dose. Further details of success criteria are provided in Section 8.3.2.
3. Treatment of interest: canakinumab 4mg/kg. Further details about the investigational treatment are provided in Section 6.

Handling of remaining intercurrent events:

1. Study treatment discontinuation after Week 8 for any reason: ignore (Treatment policy strategy)
2. Intravenous administration of corticosteroid at any time between Week 8 and Week 28: consider as non-response (Composite variable strategy)

The summary measure: Proportion of participants who are able to taper oral corticosteroids successfully at Week 28.

3 Study design

This is an open-label, single-arm active treatment study to evaluate efficacy, safety, tolerability and PK/PD of canakinumab 4 mg/kg (maximum of 300 mg) every four weeks subcutaneously administered for at least 48 weeks in Japanese participants with AOSD until canakinumab is approved and commercially available for ASD in Japan or Novartis terminates the study. Approximately 21 participants will be enrolled in the study. Enrollment was decided to be discontinued based on the feedback given by PMDA in Feb 2023.

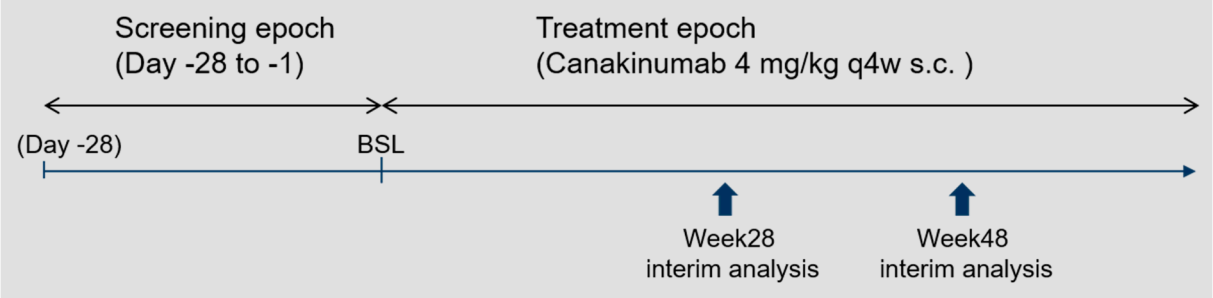
The study will consist of two distinct study epochs as outlined below (see also Figure 3-1):

- Screening epoch: Day -28 to Day -1
- Open label treatment epoch: Day 1 to approval and commercially available or study termination, whichever comes first.

Two interim analyses are planned after all participants have completed Week 28 and Week 48 to support the registration dossier in Japan. At the interim analysis at Week 28, the primary efficacy analysis will be conducted based on the data up to the time when the first 11 participants have reached Week 28 (or prematurely discontinued prior to Week 28), as per PMDA feedback received in Feb 2023.

Final analysis will be performed after all participants have completed the study.

Figure 3-1 Study design



* The primary efficacy analysis using the data up to the time when the first 11 participants have reached Week 28 (or prematurely discontinued prior to Week 28) will be performed at Week28 interim analysis.

4 Rationale

4.1 Rationale for study design

Study G1302 is an open-label, single-arm study in Japanese AOSD patients to evaluate the efficacy and safety of canakinumab 4 mg/kg (maximum 300 mg) subcutaneously administered every 4 weeks. Conducting a large-scale confirmatory trial is not feasible because the number of AOSD patients who can be enrolled in this study is limited. Regarding the rationale for an open-label study, placebo administration to AOSD participants who do not respond to corticosteroids has a safety risk of worsening the underlying disease leading to macrophage activation syndrome (MAS), a serious complication that can be fatal. Since tocilizumab is available as an approved treatment option in Japan, conducting a placebo-controlled study for AOSD participants who do not respond to corticosteroids would not be enrolled. In addition, SOC control arm of tocilizumab is not feasible, since controlled trial with tocilizumab failed and G1302 study allows participants previously treated with tocilizumab who have discontinued treatment due to safety or efficacy issues to enter study.

To compare the efficacy for Japanese AOSD and previously-treated SJIA participants, assessment time points for primary and key secondary endpoint are consistent with those evaluated in the SJIA study. Adapted ACR 30 will be assessed at Week 8 as primary endpoint. If improvements in disease activity are observed after Week 8, tapering of corticosteroid dose will be started, and the proportion of participants who have successfully reduced corticosteroid dose at Week 28 will be assessed as a key secondary endpoint.

4.2 Rationale for dose/regimen and duration of treatment

In this study, canakinumab 4 mg/kg (up to 300 mg) is to be subcutaneously administered every 4 weeks. The rationale for the dosing regimen in this study is as follows:

- This dosing regimen is identical to that for SJIA, the indication approved in Japan, which is used in patients with SJIA prolonged to ≥16 years of age in clinical setting. The data from multiple studies conducted so far in SJIA patients in Japan and foreign countries as well as the post-marketing data showed that the safety profile of canakinumab administered with this dosing regimen was favorable, and no clear differences were noted between Japanese and non-Japanese patients in PK/PD, efficacy, or safety.

- The results of SJIA pooled efficacy and safety analyses showed that the efficacy and safety of canakinumab 4 mg/kg subcutaneously administered every 4 weeks were similar across age groups, indicating the dose regimen is effective and safe regardless of age. Since SJIA and AOSD are similar diseases, similar efficacy is expected for SJIA and AOSD.
- In Study GDE01T conducted in AOSD patients using this dosing regimen, trends for greater improvement in multiple efficacy variables, such as DAS28-ESR and ACR response, were seen in the canakinumab group compared with the placebo group. Comparisons of the Study GDE01T data and the SJIA pooled dataset showed that the adapted ACR 30 response rate in canakinumab treatment was similar in AOSD and SJIA patients.
- In Study GDE01T, the safety profile of canakinumab treatment with this dosing regimen in AOSD patients was consistent with those in the SJIA pooled safety analysis results and for other approved indications, and no new safety signal was observed.
- The PK data obtained from Study GDE01T indicated that PK of canakinumab is similar in AOSD and SJIA patients across age groups (2 to <12 years, 12 to <16 years, and 16 to <20 years).

Taken together, canakinumab 4 mg/kg (up to dose 300 mg) subcutaneously administered every 4 weeks, the approved dosing regimen for SJIA patients, is considered reasonable as the dosing regimen for Japanese AOSD patients.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable.

4.4 Purpose and timing of interim analyses

Two interim analyses will be performed during this study: One will be at Week 28 to support the registration dossier and the second will be at Week 48 to supplement the dossier with long-term safety and efficacy data.

At the interim analysis at Week 28, the primary efficacy analysis will be conducted based on the data up to the time when the first 11 participants have reached Week 28 (or prematurely discontinued prior to Week 28), as per PMDA feedback received in Feb 2023.

4.5 Risks and benefits

The overall safety profile of canakinumab in AOSD patients from GDE01T study was consistent with that observed in the updated SJIA pooled dataset and with that known for canakinumab in other indications, as no new safety signals were observed.

In the Phase III canakinumab SJIA program, the most frequent adverse effects included infections, but these are usually mild to moderate, although serious infections were observed. The most frequently reported (>10%) infections, mainly affected the upper respiratory tract (nasopharyngitis, upper respiratory tract infection, rhinitis and pharyngitis) and the

gastrointestinal tract (gastroenteritis). Serious adverse events (SAEs) were mostly related with disease flares or MAS.

MAS is a well-known serious and potentially fatal condition associated with SJIA, as well as AOSD. The triggers of MAS are generally infections and disease flares. Based on the available Phase III data from SJIA studies, canakinumab neither increases nor decreases the risk of developing MAS. MAS is considered to be a potential risk also in AOSD patients, and, therefore, the clinical signs and symptoms should be carefully monitored by investigators. Potential MAS cases will be adjudicated by an independent adjudication committee on a regular basis. Occurrence of other risks, e.g., infections, neutropenia, thrombocytopenia and malignancies, are also required to be carefully monitored by the investigator.

Local tolerability at the site of subcutaneous injection will also be evaluated at all administration visits and at the end of study (EOS) visit in all patients in case of any local reaction and at each clinical visit until this has disappeared.

This study involves exposure to radiation from chest X-ray assessment for Tuberculosis (TB) screening at the screening visit. The radiation exposure by these procedures is not necessary for medical care but is intended for research purposes only to confirm participants eligibility for safety. The amount of radiation in this study is about 0.1 mSv for the X-ray procedure and is based on effective doses for various diagnostic radiological procedures reported in the literature (Mettler et al 2008). This exposure is comparable to the natural radiation an average person receives in 10 days. This radiation exposure is considered 'minimal' (Stabin et al 2009). Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure patient safety.

Women of child-bearing potential must be informed that taking the study treatment 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 requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

Participants may not be able to come to on-site visit in case of COVID-19 pandemic restrictions. If participants are unable to come to their study site for scheduled visits due to COVID-19 pandemic, investigator should contact the participant via phone call or conduct virtual contacts (e.g., teleconsult) for safety monitoring.

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

Canakinumab is known to be highly effective and safe for patients with SJIA which is a similar disease to AOSD. Data from the pooled analysis of clinical trials in SJIA patients demonstrate similar efficacy and safety profiles of canakinumab throughout the age groups (2 to <12 years, 12 to <16 years, and 16 to <20 years). ≥70% of SJIA participants achieved adapted ACR Pediatric 30 response across age groups at Day 15, and the response rate remained similar across age groups until Day 85. An investigator-initiated trial in non-Japanese AOSD patients (Study GDE01T) consistently showed trends toward greater improvement in efficacy endpoints, such as improvement in DAS28-ESR and ACR response rate, in the canakinumab group compared with the placebo group, although statistical significance was not achieved. Additionally, a

comparison of the Study GDE01T data and the SJIA pooled dataset showed that the adapted ACR 30 response rate in canakinumab treatment was similar in AOSD and SJIA patients. Taken together, canakinumab was considered effective for AOSD as well as for SJIA.

4.6 Rationale for Public Health Emergency mitigation procedures

During a public health emergency as declared by local or regional authorities e.g., pandemic, epidemic, or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

5 Study Population

The study population will consist of male / female participants with a confirmed diagnosis of AOSD (≥16 years of age) who had inadequate response to corticosteroid therapy.

It is planned to enroll approximately 21 participants. Enrollment was decided to be discontinued based on the feedback given by PMDA in Feb 2023.

It is expected that the screen failure rate will be around 30% therefore approximately 30 participants may need to be screened in order to complete recruitment.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study. Parent's or legal guardian's written informed consent and child's assent, if appropriate, are required before any assessment is performed for participants < 20 years of age
2. Japanese male / female participants aged ≥ 16 years
3. Confirmed diagnosis of AOSD as per Yamaguchi criteria (Yamaguchi M, 1992) with an onset of disease ≥ 16 years of age. Yamaguchi criteria requires at least five criteria, including two major criteria and no exclusion criteria:

   Major criteria

   - Fever ≥ 39 °C lasting 1 week or more
   - Arthralgia lasting 2 weeks or more
   - Typical skin rash: maculopapular, nonpruritic, salmon-pink rash with concomitant fever spikes
   - Leukocytosis ≥10,000/mm^3 with neutrophil polymorphonuclear proportion ≥ 80%

   Minor criteria

   - Pharyngitis or sore throat

- Lymphadenopathy and/or splenomegaly
- Liver enzyme abnormalities
- Negative for RF or antinuclear antibodies

Exclusion criteria

- Infection, especially sepsis and Epstein–Barr viral infection
- Malignant diseases, especially malignant lymphomas
- Inflammatory disease, especially polyarteritis nodosa

4. Active disease at the time of baseline defined as follows
   - Fever (body temperature > 38°C) due to AOSD for at least 1 day within 1 week before baseline
   - At least 2 active joints (tender or swollen)
   - CRP ≥ 10 mg/L
5. Participants who have history of inadequate response to more than 2 weeks of corticosteroids equivalent to at least 0.4 mg/kg/day of prednisolone

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study

1. Pregnant or nursing (lactating) female participants, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/ mL) at screening visit
2. For female participants of child-bearing potential defined as all females physiologically capable of becoming pregnant, unless they are using effective methods of contraception during administration of study treatment. Effective contraception methods include:
   - Barrier methods of contraception: male or female condom or occlusive cap, diaphragm or cervical/vault caps.
   - Other more effective forms such as oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or total abstinence or male/female sterilization

   Note: Women of non-childbearing potential is defined as women who are physiologically and/or anatomically incapable of becoming pregnant, as now further described:
   - They are post-menopausal as evidenced by 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age appropriate history of vasomotor symptoms).
   - They have had bilateral surgical oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the informed consent form (ICF).

3. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
4. History of significant hypersensitivity to study drug or to biologics.
5. History/evidence of active MAS or disseminated intravascular coagulation (DIC) within 6 months of enrollment.
6. With underlying metabolic, renal, hepatic, infectious or gastrointestinal conditions which in the opinion of the investigator compromises the participant and/ or places the participant at unacceptable risk for participation in an immunomodulatory therapy.
7. Clinical evidence of liver disease or liver injury as indicated by abnormal liver function tests at screening such as Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP)(must not exceed 3 times the upper limit value of the normal range for age), or serum bilirubin (must not exceed twice the upper limit value of the normal range for age). Exception: participants who exceed this limit after initiating latent TB treatment may be eligible for participation in this study pending confirmation with Novartis.
8. Presence of moderate to severe impaired renal function as indicated by clinically significantly abnormal creatinine (≥ 1.5 x upper normal limit ULN) or abnormal urinary constituents (e.g., albuminuria) at screening. Evidence of urinary obstruction or difficulty in voiding at screening.
9. Use of concomitant treatments including disease-modifying and/or immunosuppressive drugs with the exception of:
    - Stable daily dose of systemic corticosteroid treatment ≥ 10 mg AND ≤ 1.0 mg/kg/day (maximum 60 mg/day) of oral prednisone (or equivalent) for at least 1 week prior to baseline
    - Stable dose of no more than one non-steroidal anti-inflammatory drug (NSAID) for at least 1 week prior to the baseline visit
    - Stable dose of methotrexate (maximum of 20 mg/m^2/week) for at least 4 weeks prior to the baseline visit, and folic/folinic acid supplementation (according to standard medical practice of the center)
10. Use of following therapies:
    - Anakinra within 24 hours prior to baseline visit
    - Rilonacept within 1 week prior to baseline visit
    - Tocilizumab within 3 weeks prior baseline
    - Etanercept within 4 weeks prior baseline
    - Infliximab within 12 weeks prior to the baseline visit
    - Golimumab within 12 weeks prior to the baseline visit
    - Adalimumab within 8 weeks prior to the baseline visit
    - Abatacept within 10 weeks prior to the baseline visit
    - Rituximab within 26 weeks prior to the baseline visit

- Leflunomide within 4 weeks prior to the baseline visit. Documentation of a completion of a full cholestyramine elimination treatment after most recent leflunomide use will be required.
- Certolizumab pegol within 12 weeks prior to the baseline visit
- Cyclosporine within 4 weeks prior to the baseline visit
- Tacrolimus within 2 weeks prior to baseline visit
- Intravenous immunoglobulin (i.v. Ig) prior to 8 weeks prior to the baseline visit
- 6-Mercaptopurine, azathioprine, cyclophosphamide, or chlorambucil prior to 12 weeks prior to the baseline visit
- Dapsone, mycophenolate mofetil within 3 weeks prior to the baseline visit
- Intra-articular, peri-articular, or intramuscular corticosteroid injections within 4 weeks prior to the baseline visit.

11. Positive TB screening test (chest X-ray and Quantiferon TB test) at screening visit or within 4 weeks prior to the screening visit. Participants with a positive TB screening test are eligible to participate in the study if (1) active TB is ruled out and (2) the participant is willing and able to complete a minimum of 4 weeks of latent TB treatment prior to initiating treatment with canakinumab (Day 1) and (3) the participant is willing to continue and complete the latent TB treatment (according to local guidelines) in parallel with study treatments. Participants diagnosed with active TB should be referred for treatment as deemed appropriate and are not eligible to participate in this study.
12. With active or recurrent bacterial, fungal or viral infection at the time of enrollment, including participants with evidence of Human Immunodeficiency Virus (HIV) infection, Hepatitis B and Hepatitis C infection.
13. Any of the risk factors for TB such as:
    - History of any of the following: residence in a congregate setting (e.g., jail or prison, homeless shelter, or chronic care facility), substance abuse (e.g., injection or no injection); health-care workers with unprotected exposure to participants who are at high risk of TB or participants with TB disease before the identification and correct airborne precautions of the participant, or
    - Close contact (i.e., share the same air space in a household or other enclosed environment for a prolonged period (days or weeks, not minutes or hours)) with a person with active pulmonary TB disease within the last year
    - Evidence of Latent TB (positive Quantiferon TB test) but unwilling or unable to complete a minimum of 4 weeks of latent TB treatment before initiating treatment with canakinumab (Day 1).
14. Participants with absolute neutrophil count < $1500/mm^3$ at screening.
15. History or current diagnosis of ECG abnormalities indicating significant risk of safety for participants participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or known family history of Torsades de Pointes

16. History of malignancy of any organ system, treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases, with the exception of localized excised non-melanomatous skin lesions.
17. Live vaccinations within 3 months prior to the start of the study. Killed or inactivated vaccines may be permitted according to the investigator's discretion.
18. Familial and social conditions rendering regular medical assessment not possible
19. History of drug or alcohol abuse within the 12 months prior to dosing

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Participants will receive canakinumab 4 mg/kg (maximum of 300 mg) administered subcutaneously every 4 weeks at the study site throughout the study.

ACZ885 150 mg: Active canakinumab in individual 2 mL glass vials, each containing 150 mg canakinumab liquid in vial (Table 6-1).

Table 6-1 Investigational drug

Investigational Drug	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
ACZ885 150 mg	Solution for Injection	Subcutaneous Injection	Open label supply in vials	Sponsor (global)

The maximal total single dose of canakinumab allowed is 300 mg in one day, which is administered as two subcutaneous 150 mg injections once every 4 weeks.

Novartis will provide canakinumab until canakinumab is approved for ASD in Japan or Novartis terminates the study.

6.1.2 Additional study treatments

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

6.1.3 Supply of study treatment

Not applicable.

6.1.4 Treatment arms/group

All participants will receive canakinumab as open-label study medication.

Participants will be administered canakinumab 4 mg/kg every 4 weeks. The maximum total single dose of canakinumab allowed is 300 mg. Any participant who requires a dose greater than a single dose of 150 mg (participants > 37.5 kg) will require two s.c. injections.

6.1.5 Treatment duration

The planned duration of treatment is at least 48 weeks. The study allows participants to continue canakinumab treatment until it is approved for ASD and is commercially available for clinical use in Japan or Novartis terminates the study. Participants may be discontinued from treatment earlier due to unacceptable adverse event (AE), disease progression and/or treatment is discontinued at the discretion of the investigator or the participant.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

No concomitant use of second line agents such as disease-modifying and/or immunosuppressive drugs will be allowed with the exception of followings:

- Systemic corticosteroid treatment ≤ 1.0 mg/kg/day (maximum 60 mg/day) in 1-2 doses of oral prednisone (or equivalent). Daily dose of systemic corticosteroid treatment (≥ 10 mg AND ≤ 1.0 mg/kg/day, maximum 60 mg/day) should be stable until Week 8. Beginning at the Week 8 visit, corticosteroid dose tapering should be attempted as per corticosteroid tapering guidelines.
- Stable dose of methotrexate (maximum of 20 mg/m^2/ week) and folic/folinic acid supplementation (according to standard medical practice of the center).
- Stable dose of no more than one NSAID.

Corticosteroid tapering

Participants using concomitant corticosteroids at study entry may begin to reduce their corticosteroid dose to the lowest possible dose/discontinuation beginning at Week 8 until the End of Study. All changes in corticosteroid doses should be made in the appropriate concomitant medication eCRF.

Rules for corticosteroid tapering:

- Corticosteroid tapering is encouraged and permitted to occur beginning at Week 8 if it is the investigator's judgment that a participant's AOSD disease activity is stable and has not worsened.
- As shown in Table 6-2, for oral prednisone (or equivalent) doses > 0.1 mg/kg/day, the dose should be tapered at 0.1 mg/kg of oral prednisone (or equivalent) per week. If and

when the oral prednisone (or equivalent) dose is at 0.1 mg/kg/day, the dose should be reduced to 0.05 mg/kg/day of oral prednisone (or equivalent) for 1 week, then to ≤0.05 mg/kg/every 48 hours for the next 2 weeks and then discontinued.

- If it is the investigator's judgment that a participant's AOSD disease activity worsens during corticosteroid tapering then the participant must return to the immediate prior dose (or higher if deemed necessary by the investigator) and may not resume corticosteroid dose tapering for at least 2 weeks.

Table 6-2 Corticosteroid tapering guideline

Prednisone (or equivalent) dose	Amount of reduction
> 0.1 mg/kg/day	Taper at 0.1 mg/kg per week until at dose of 0.1 mg/kg/day
0.1 mg/kg/day	Taper to dose of 0.05 mg/kg/day for 1 week
≤ 0.05 mg/kg/day	Alternate administration days (i.e. take dose every 48 hours) for 2 weeks and then discontinue

6.2.2 Prohibited medication

Use of the treatments displayed in Table 6-3 are not allowed after the start of study treatment.

Table 6-3 Prohibited medication

Medication	Prohibition period	Action taken
Anakinra	during treatment period	Discontinue study treatment
Tocilizumab, abatacept, rilonacept , rituximab and any other biologics (investigational or marketed)	during treatment period	Discontinue study treatment
Etanercept, adalimumab, infliximab, or any TNF inhibitor (investigational or marketed)	during treatment period	Discontinue study treatment
Oral JAK inhibitor	during treatment period	Discontinue study treatment
Leflunomide, thalidomide, cyclosporine, tacrolimus, or i.v. immunoglobulin (i.v. Ig)	during treatment period	Discontinue study treatment
6-Merceptopurine, azathioprine, cyclophosphamide, or chlorambucil	during treatment period	Discontinue study treatment
Dapsone or mycophenolate mofetil	during treatment period	Discontinue study treatment
Intra-articular, peri-articular or intramuscular corticosteroid injections	during treatment period	Discontinue study treatment
Any other investigational non-biological drugs	during treatment period	Discontinue study treatment
Live vaccination	during treatment period	Discontinue study treatment

6.2.3 Rescue medication

Rescue medication will not be allowed during the course of the study.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational (Section 6.1.1).

Detailed instructions on the preparation and administration of the study drug will be described in the pharmacist instruction manual and provided to each site. A unique medication number is printed on the study medication label.

6.3.1 Handling of study treatment and additional treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified in the Investigator's Brochure.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in Japanese and comply with the legal requirements of Japan. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

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

6.3.2 Instruction for prescribing and taking study treatment

The s.c. injections of investigational treatment may be administered into the participant's arm or abdomen or thigh. Detailed instructions on the preparation and administration of the study drug will be described in the Pharmacist Manual and provided to each site.

All participants will receive a first open-label canakinumab 4 mg/kg (maximum of 300 mg) s.c. at Baseline (Day 1).

Following Baseline, patients will receive injections every 4 weeks until canakinumab is approved for ASD in Japan and commercially available or until Novartis terminates the study.

All dosages administered to the participant and all dose changes during the study must be recorded on the appropriate CRF.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available. A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.4.2 Treatment assignment, randomization

No randomization and assignment will be performed in this study.

6.5 Treatment blinding

Treatment will be open to participants, investigator staff, persons performing the assessments, and the Clinical Trial Team (CTT).

6.6 Dose escalation and dose modification

Investigational study treatment dose adjustments are not permitted. Study treatment interruption is only permitted if, in the opinion of the investigator, a subject is deemed to be placed at a significant safety risk unless dosing is temporarily interrupted. In such cases, study treatment should be interrupted only during the time that this risk is present and ongoing. Study treatment can be restarted at the next scheduled visit after resolution of the safety risk. Any study treatment interruption must be recorded on the appropriate eCRF.

6.6.1 Dose modifications

Study treatment dose modifications are not allowed.

6.6.2 Follow-up for toxicities

Not applicable.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

Any deviations from the protocol regarding the administration of study medication must be described on the appropriate CRF. Concomitant medications/ non-drug therapy before the first dose of study medication and after start of study drug will be collected, including medication name and reason. Compliance is expected to be 100% since study drug will be administered by the investigator or study personnel.

6.7.2 Recommended treatment of adverse events

AE should be treated according to local practice and guidelines, and is at the discretion of the investigator and treating physician.

Medication used to treat AEs must be recorded on the appropriate CRF.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation) Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

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

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant 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 participant.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants who took study treatment

Women of child bearing potential must be informed that taking the study treatment 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 requirements.

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

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

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

7.1 Pediatric Assent

In pediatric participants (< 20 years of age) parental permission and, whenever possible, pediatric assent is needed instead of the procedure for informed consent used for research involving adults. In general, one or both parents or a guardian must be provided with the information ordinarily required for informed consent, so that they may decide whether to allow the child to participate, and children capable of assent must also express their willingness to participate. These forms will be submitted for IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

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

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AE and concomitant medications not previously reported must be recorded on the CRF.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing

staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Period	**Screening**	**Treatment**																
Visit Name	**Screening**	**Baseline**	**Day3**	**Day 15**	**Week 4**	**Week 8**	**Week12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week48**	**Week 52,56,...**	**EOS**
Days	**-28 to -1**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**Every 4weeks**	**9999**
Informed consent	X																	
Demography	X																	
Inclusion / Exclusion criteria	X	X																
Prior medications and therapies	X																	
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history/current medical conditions	X																	
Hepatitis screen	S																	
HIV screen	S																	
Chest X-ray	X																	
QuantiFERON TB test	X																	
Physical Examination	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Body Height	X																	
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Pressure and Pulse Rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	**Screening**	**Treatment**																
Visit Name	**Screening**	**Baseline**	**Day3**	**Day 15**	**Week 4**	**Week 8**	**Week12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week48**	**Week 52,56,...**	**EOS**
Days	**-28 to -1**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**Every 4weeks**	**9999**
Electrocardiogram (ECG)	X									X						X	X[1]	X
Physician's global assessment of disease activity (VAS)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[2]	X
Participant's global assessment of disease activity (VAS)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[2]	X
Health Assessment Questionnaire (HAQ)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[2]	X
Tender and swollen joint counts		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[2]	X
CRP (local lab)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fever assessment[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adapted ACR response assessment[3]				X	X	X	X	X	X	X	X	X	X	X	X	X	X[2]	X
DAS28-CRP		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X[2]	X
Systemic feature score[3,4]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X[2]	X
Rash assessment		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																		

Period	**Screening**	**Treatment**																
Visit Name	**Screening**	**Baseline**	**Day3**	**Day 15**	**Week 4**	**Week 8**	**Week12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week48**	**Week 52,56,...**	**EOS**
Days	**-28 to -1**	**1**	**3**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**Every 4weeks**	**9999**
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ESR		X	X	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	X	X	X	X
Pregnancy and assessments of fertility[6]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Study drug administration		X			X	X	X	X	X	X	X	X	X	X	X	X	X	
PK (canakinumab)		X	X	X	X		X			X			X			X	X[2]	
PD (total IL-1β)		X	X	X	X		X			X			X			X	X[2]	
Anti-drug antibody in blood		X								X						X	X[1]	
CCI																		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local tolerability		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial Feedback Questionnaire		X								X								X
Study completion information																		X

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
1 Every 24 weeks
2 Every 12 weeks
3 Fever will be recorded in the diary and used for Adapted ACR response assessment and Systemic feature score.
4 Ultrasound sonography for liver and spleen must be performed at Baseline, Week 28, Week 48 and EOS visit. At other visits, palpation will be performed. In case investigator confirmed any findings of hepatomegaly/splenomegaly by palpation, perform ultrasound sonography.
5 Ferritin and fibrinogen will be measured at dosing visits and in case of suspicion of MAS by the investigator.
6 Serum pregnancy test is required at Screening. Urine pregnancy tests will be performed at each visit after Baseline visit.

8.1 Screening

Screening

It is permissible to re-screen a participant once if she/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. Re-screening should only occur after a participant has failed screening. For re-screening, all screening assessments must be performed as per protocol (see Table 8-1) and the subject must sign a new informed consent form. Re-screened subjects should be assigned a new subject ID number. If no screening assessments are performed on the day of informed consent, the screening assessments must be completed within 28 days from the date of the first screening assessment performed after the date of informed consent.

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a SAE during the screening epoch (see Section 10.1.3 for reporting details).

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

At screening visit, participant demographic and baseline characteristic data to be collected on all participants include: age, sex, race, ethnicity. Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities. In addition, relevant medical history and current medical conditions at screening, a full physical examination, vital signs and a pregnancy test (when applicable) will also be performed. Where possible, diagnoses and not symptoms will be recorded.

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

Confirmed diagnosis of AOSD as per Yamaguchi's criteria (Yamaguchi, et al 1992) with the date of disease onset and history and diagnosis of AOSD will be recorded on the relevant eCRF page at Screening (Visit 1).

8.2.1 Hepatitis screen, HIV screen

In order to exclude an active infection such as hepatitis or HIV infection, all participants will undergo appropriate testing at the Screening visit. Participants will be screened for HBsAg, anti-HBs antibody, and anti-HBc antibody. Screening for Hepatitis C will be based on anti-

HCV antibodies. A copy of the lab report must be placed in the participant's file. 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 subject counseling will be made available by the investigator in the event of a positive finding. A copy of the laboratory report must be placed in the participant's file.

8.2.2 Tuberculosis screening

TB screen will be performed at screening before the first dose of study medication to evaluate an eventual infection with TB.

8.2.2.1 Chest X-ray

A chest X-ray must be performed as part of TB screening for all participants at the Screening Visit. In cases where a negative result is available within 4 weeks prior to screening and the investigator has no suspicion of change in the participant's TB risk in the interval, an additional chest X-ray test is not required at Screening.

8.2.2.2 Quantiferon TB test

Quantiferon TB test must be performed for all participants at the Screening Visit. In cases where a negative result is available within 4 weeks prior to screening and the investigator has no suspicion of infection since the negative Quantiferon TB test (e.g., the participant has not been exposed to any external factors that might have caused an infection), an additional Quantiferon TB test is not required at Screening. Details about sample processing are described in the central laboratory manual. Participants with a negative Quantiferon TB will be eligible for study entry. In case of a positive Quantiferon TB test result, the investigator will, according to local guidance, perform a TB workup to evaluate the participant for active / latent TB infection (Note: A repeat TB [Quantiferon TB or PPD] test should not be performed as part of the TB workup). Participants with active TB should be referred for treatment as deemed appropriate and are not eligible to participate in this study. Participants with latent TB are eligible for participation in the study upon completing a minimum of 4 weeks of treatment (according to local guidelines) for latent TB, provided that the participant is willing to continue and complete the treatment (according to local guidelines) in parallel with study treatment. In case of an indeterminate Quantiferon TB test result, one repeat Quantiferon TB test may be performed. If the result of the repeat test is also indeterminate, for the purpose of this study, the participant will be handled as if the test result was positive (i.e., the investigator should perform a TB workup as per local guidelines). Any significant findings will be recorded in the Relevant Medical History/Current Medical Conditions section of the eCRF as necessary.

8.3 Efficacy

8.3.1 Adapted ACR criteria

Adapted ACR30 response is defined as 30% reduction between baseline and post-baseline values in at least 3 of the 5 response variables 1 to 5 and no intermittent fever in the preceding week (variable 6), with no more than one of variables 1-5 worsening by more than 30%:

1. Physician's global assessment of disease activity

2. Participant's assessment of disease activity (Participant's overall well-being)
3. Functional ability assessed using Health Assessment Questionnaire (HAQ)
4. Number of active joints (68 joints evaluated for pain/tenderness and 66 for swelling)
5. Laboratory measure of inflammation: CRP (mg/L)
6. Absence of intermittent fever in the preceding week

The adapted ACR response variables will be assessed at the scheduled visits as shown in Table 8-1.The adapted ACR 50, 70, 90 and 100 criteria will be used as additional efficacy assessments, i.e., an improvement ≥ 50%, ≥ 70%, ≥ 90%, or = 100% in at least 3 of 5 response variables and no intermittent fever in the preceding week (variable 6) with no more than one variable of 1-5 worsening by more than 30%.

8.3.1.1 Physician's global assessment of disease activity (VAS)

The physician will rate the participant's current condition on a 0-100 mm Visual Analog Scale (VAS), ranging from no disease activity (0 mm) to very severe disease activity (100 mm). Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left and the value will be entered on the tablet device. To enhance objectivity, the physician must not be aware of the specific participant's global assessment of participant's overall well-being, when performing his own assessment on that participant.

8.3.1.2 Participant's assessments of disease activity (Participant's overall well-being /Pain) on a 0-100 mm (VAS)

Two type of participant's assessments of disease activity (participant's overall well-being and pain) will be assessed on the VAS in the tablet device. Participant's assessments of disease activity regarding participant's overall well-being is one of the adapted ACR criteria. The VAS scale ranges from 0-100 mm, from very well (0 mm) to very poor (100 mm) for overall well-being and from no pain (0 mm) to very severe pain (100 mm) for pain respectively. Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left.

8.3.1.3 Health Assessment Questionnaire (HAQ)

The health assessment questionnaire, HAQ©, will be used to assess physical ability and functional status of participants as well as quality of life. The disability dimension consists of 20 multiple choice items concerning difficulty in performing eight common activities of daily living; dressing, arising, eating, walking, hygiene, reach, grip and usual activities. Participants choose from four response categories, ranging from 'without any difficulty' to 'unable to do'. This questionnaire should be completed by the participant on the tablet device. A detailed tablet device Site Manual describing the administrative procedures of the HAQ questionnaire will be given to the sites.

8.3.1.4 Number of active joints (tender or swollen joints)

Active joints are defined as joints with swelling or pain/tenderness. 68 joints will be assessed for tenderness and 66 joints for swelling.

For there to be consistency between the joint assessments, it is strongly recommended that the same evaluator perform these assessments at all visits.

8.3.1.5 C-reactive protein (CRP)

C-reactive protein will be determined in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment. Analytes will be measured at the local lab. The actual sample collection date and time and result will be entered on the tablet device.

8.3.1.6 Fever assessment

The absence or presence of intermittent fever due to AOSD (oral, rectal, or axillary body temperature > 38°C only for several hours during the day) will be assessed. Participant diary will be dispensed to the participants at each visit to record fever from the occurrence to one day after resolution.

8.3.2 Corticosteroid tapering

Participants using concomitant corticosteroids at study entry may begin to reduce their corticosteroid dose to the lowest possible dose/discontinuation beginning at Week 8 until the End of Study as detailed in Section 6.2.1.1 of the protocol.

Successful oral corticosteroid tapering is defined as meeting one of the following:

- Participants with prednisone equivalent dose of > 0.8 mg/kg/day at baseline were able to reduce their dose to ≤ 0.5 mg/kg/day.
- Participants with prednisone equivalent dose from ≥ 0.5 mg/kg/day and ≤ 0.8 mg/kg/day at baseline were able to reduce their dose by at least 0.3 mg/kg/day.
- Participants with any initial prednisone equivalent dose at baseline were able to reduce their dose to ≤ 0.2 mg/kg/day.
- Participants with prednisone equivalent dose of ≤ 0.2 mg/kg/day at baseline were able to reduce their dose with any reduction

AND maintaining a minimum adapted ACR30 response.

8.3.3 Rash assessment

Rash is one of major clinical symptoms of AOSD and typically a salmon-colored rash that occurs along with onset of fever but is transient and disappears at normal body temperature.

The absence or presence of skin rash will be assessed based on physical exam findings including whether it is typical or atypical.

8.3.4 Systemic feature score

Systemic feature score consists of 5 clinical and 5 laboratory assessments. Clinical features include fever, rash, lymphadenopathy, hepatosplenomegaly and serositis. Laboratory features include erythrocyte sedimentation rate, C reactive protein, leucocyte count, hemoglobin level

and platelet count. Each clinical and laboratory feature will be assigned a score of 1 (present) or 0 (absent):

- Fever [defined as a body temperature >37.5°C at least once a day during at least 5 consecutive days]
- Rash [defined by the presence of typical salmon-pink rash on the trunk and elsewhere during the febrile episodes]
- Serositis,
- Lymphadenopathy [defined by lymph node enlargement to >1.5 cm localized anywhere within the body]
- Hepatomegaly and/or splenomegaly that had been confirmed by ultrasound evaluation

Note: Ultrasound sonography for liver and spleen must be performed at baseline, Week 28, Week 48 and EOS visit to assess the presence of hepatomegaly and splenomegaly.

At other assessment visits, palpation will be performed. In case investigator confirmed any findings of hepatomegaly/splenomegaly by palpation, perform ultrasound sonography. If no finding regarding hepatomegaly or splenomegaly is confirmed by palpation, hepatomegaly/splenomegaly is evaluated as "absent". If there are any findings by palpation but ultrasound sonography is not performed, then hepatomegaly/splenomegaly will be evaluated as "present".

At baseline, laboratory features were considered present based on the following:

- ESR ≥20 mm/hour
- CRP ≥10 mg/liter
- White blood cell (WBC) count ≥12 x 10^9/liter
- Hemoglobin ≤11 g/dl
- Platelet count ≥400 x 10^9/liter.

During treatment epochs and at follow up visits, the laboratory parameters were scored as follows:

- ESR, score of 0 if <20 mm/hour or if decreased by ≥30% compared to baseline, score of 1 if increased or if decreased by <30% compared to baseline
- CRP, score of 0 if <10 mg/liter or if decreased by ≥30% compared to baseline, score of 1 if increased or if decreased by <30%
- WBC count, score of 0 if <12 x 10^9/liter or if decreased by ≥20% compared to baseline, score of 1 if increased or if decreased by <20%
- Hemoglobin level, score of 0 if >11 g/dl or if increased by ≥20% compared to baseline, but score of 1 if decreased or if increased by <20%;
- Platelet count, score of 0 if <400 x 10^9/liter or if decreased by ≥20% compared to baseline, score of 1 if increased or if decreased by <20%.

8.3.5 DAS28-CRP

The DAS28-CRP is a measure of disease activity in Rheumatoid arthritis (RA) based on Swollen and Tender Joints Counts (out of a total of 28), CRP and the Patient's Global

Assessment of Disease (Prevoo et al 1995; Fransen et al 2003). DAS28-CRP is a composite index, validated for RA patients and takes into account the following items: Tender joint count (number of tender joints; 0-28); swollen joint count (number of swollen joints; 0-28); C-reactive protein (mg/l) and Global Health (Patient's Global Assessment of Disease Activity; from 0=best to 100=worst). Thus, given the reliability, validity, and ability of DAS28 to discriminate the severity of joint involvement, this index has been used in other rheumatic diseases characterized by RA-like poly-articular involvement. Of note, a DAS28 score > 5.1 implies active disease, ≤3.2 low disease activity, and <2.6 remission. Moderate/high disease activity is defined as a DAS28 higher than 3.2.

8.3.6 Appropriateness of efficacy assessments

AOSD is primarily characterized by systemic (including fever) and joint symptoms, and therefore both should be evaluated to assess the therapeutic effect. At this point, however, there are no established measures for systemic symptoms and joint symptoms of AOSD. The adapted ACR Pediatric criteria, which was used in previous Canakinumab clinical trial for SJIA, includes physician/patient's global assessment, patient-reported outcomes, joint assessment, CRP, and presence/absence of fever and enables a comprehensive assessment of systemic symptoms and joint symptoms. The adapted ACR Pediatric criteria are based on the Juvenile Idiopathic Arthritis (JIA) core set developed by the International Leagues of Associations for Rheumatism, and the JIA clinical assessment guideline issued by EMA (EMA 2015) also recommends selecting them as the primary efficacy endpoint.

Among the criteria included in the adapted ACR Pediatric criteria, joints with limitation of motion is characteristic to pediatric assessment. When joint symptoms are assessed in adult patients, including patients with AOSD or RA, in a clinical setting, the presence of tender and/or swollen joints is assessed, whereas limited range of joint motion is not assessed. In consideration of the minor difference in the joint assessment methods between pediatric and adult patients, a total of 6 criteria from the adapted ACR Pediatric criteria, excluding the number of joints with limitation of motion, will be included in the adapted ACR criteria used in this study.

While corticosteroids are the first-line therapy for the treatment of AOSD, reduction of corticosteroid use is desired due to its adverse drug reactions due to long-term use. Therefore, the proportion of patients who achieve reduction of a corticosteroid dose successfully will be assessed as the key secondary endpoint in this study.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an AE must be recorded as an AE.
Vital signs	Vital signs will include measurement of participant's body temperature, blood pressure (BP) and pulse. Body temperature (axillary, oral, or rectal) will be measured by the Investigator at each visit. In addition, participant will measure body temperature axillary, orally or rectally during occurrence of fever and record it in the participant's diary from the occurrence until one day after resolution. Systolic and diastolic BP and radial pulse rate will be assessed after the participant has rested in the supine position for at least 3 minutes. BP should be assessed on the same arm each time measurements are taken. These data will be recorded in the eCRF. At the baseline visit, a triplicate blood pressure measuring technique will be implemented. Systolic and diastolic blood pressure will be measured three times. The repeat sitting measurements will be made at 1-2 min intervals and the mean of the three measurements will be used. Clinically notable vital signs are defined in Appendix 1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as indicated in Table 8-1 If possible, body weight assessments should be performed by the same study site staff member and using the same scale throughout the study.

8.4.1 Laboratory evaluations

If participants cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits.

Clinically notable laboratory findings are defined in Appendix 1.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or AEs as appropriate.

Table 8-2 List of laboratory parameters

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Erythrocytes, Leukocytes , Erythrocyte Cell Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other)
Chemistry	Albumin, ALP, ALT , AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphate, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL Cholesterol, HDL Cholesterol, Total Protein, Triglycerides, Urea Nitrogen or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting), ferritin, fibrinogen, CRP, ESR, Prothrombin Time/International Normalized Ratio (PT/INR), Glutamate dehydrogenase(GLDH) Ferritin and fibrinogen will be also measured in cases of suspicion of MAS by the investigator. Regarding CRP also see Section 8.3.1.5. ESR will be measured at local laboratory. PT/INR and GLDH will be measured in case of liver event (See Section 10.2.1)
Urinalysis	Microscopic Panel (Erythrocytes, Leukocytes and Casts) Macroscopic Panel (Dipstick) (Bilirubin, Occult Blood, Glucose, Ketones, Leukocytes esterase, pH, Protein, Specific Gravity) In case blood and/or leukocytes, and/or protein show traces/values in the 'dipstick' evaluation at the site, a macroscopic and microscopic examination including RBC, WBC, and casts will be performed at the central lab.
Hepatitis markers	Hepatitis B Virus DNA, Hepatitis B Virus Surface Antigen, Hepatitis B Virus Surface Antibody, Hepatitis B Virus Core Antibody, anti-HCV (baseline)
Additional test	HIV test
Pregnancy Test	Serum / Urine pregnancy test (refer to 'Pregnancy and assessments of fertility' Section 8.4.3)

8.4.2 Electrocardiogram (ECG)

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The QT interval corrected by Fridericia's formula (QTcF) should be used for clinical decisions.

Single 12-lead ECGs are collected. The original ECGs on non-heat-sensitive paper or a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

Any identifier details must be redacted, e.g., participant initials, date of birth.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or AEs as appropriate.

8.4.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Female participants of child-bearing potential must be informed of the need to prevent pregnancy during the study. Please refer to Section 5.2 for effective contraception methods. A

serum pregnancy test is required at Screening. Urine pregnancy tests will be performed as indicated in Table 8-1.

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

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, Follicle Stimulating Hormone (FSH) testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Other safety evaluations

Local tolerability

Local tolerability at the site of subcutaneous injection will be evaluated by a physician at each administration visit starting from Day 1 after study drug administration and, in case of any local reaction, at each clinical visit until it has disappeared.

Macrophage Activation Syndrome (MAS)

Occurrence of biologic features of MAS such as hemorrhages, central nervous system dysfunction, hepatomegaly, serum fibrinogen level < 2.5 g/L, cytopenia, hypertriglyceridemia, decreased platelet count, increased aspartate transaminase, hyperferritinemia (Ravelli et al 2005) must be carefully monitored by the investigator. Significant findings which meet the definition must be recorded in the Adverse Event eCRF for subsequent adjudication by the MAS Adjudication Committee.

8.4.5 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Trial Feedback

Trials have an option of including an anonymized questionnaire, 'Trial Feedback Questionnaire' for participants to provide feedback on their clinical trial experience. Individual participant level responses will not be reviewed by investigators. Responses would be used by the sponsor (Novartis) to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the participant's disease, symptoms, treatment effect or AEs and therefore would not be trial data. Should any spontaneous information be collected about AEs, this would be transferred to the safety database.

8.5.2 Pharmacokinetics (PK), immunogenicity (IG) and pharmacodynamic (PD) assessments

PK, IG and PD samples will be collected at the visits defined in the assessment schedule (Table 8-1). Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information.

The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

PK samples will be obtained pre-dose of ACZ885 and evaluated in all participants at all dose levels. Whole blood samples will be collected and serum samples will be analyzed to characterize the disposition of ACZ885. The detailed method description to assess canakinumab concentration will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR).

The anti-drug antibodies (ADAs) against canakinumab will be assessed in serum using a validated immunoassay assay. Details of the method will be provided in the BDR.

Total IL-1β (sum of IL-1β free and bound to canakinumab) will be assessed. Details of the analytical methods to assess total IL-1β in serum will be described in the BDR.

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study treatment administration, if any) and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which continued study participation might result in a safety risk to the participant
- Any severe or serious adverse event that is not compatible with administration of study medication, including adverse events that require treatment with an unacceptable co-medication
- Onset of malignancy
- Occurrence of uncontrolled life-threatening infection
- Any other protocol deviation that results in a significant risk to the participant’s safety

The investigator should consider discontinuing participants from study treatment who experience a clinically important worsening of disease activity compared to baseline at two consecutive visits after Week 4. A clinically important worsening will be defined as participants who do not meet the adapted ACR30 criteria by Week 12 or participants with non-response (defined as Adapted ACR <30) at two consecutive visits at any time in the study beginning at Week 12.

All participants who discontinue will complete an EOS visit, be discontinued from the trial and be treated as per standard local medical practice (see also Section 10.1.3 for information on SAE reporting following the last dose of study medication).

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant’s discontinuation from study treatment and record this information.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer to Section 8).

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

9.1.2 Discontinuation from study

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

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

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

9.2 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments(including further study-related contacts)

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to study discontinuation.

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 participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise of data privacy rights should be made as detailed in Section 8.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.3 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

All treated participants should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment: participants will complete an EOS visit. 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 participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

The investigator has the responsibility for managing the safety of individual participant and identifying AEs.

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

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

AEs must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

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. The causality

The investigator is obligated to assess the relationship between any treatment used in the study (study treatment) and each occurrence of each AE. The investigator will use clinical judgment to determine the relationship. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

AE Reporting via an Electronic Data Collection Tool

The primary mechanism for reporting an AE to Novartis will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper AE data collection tool (see next section) to report the event.

The site will enter the AE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new AE from a study participant or receives updated data on a previously reported AE after the electronic data collection tool has been taken offline, then the site can report this information on a paper AE form (see next section) or by telephone.

AE Reporting via Paper Data Collection Tool

Facsimile transmission of the AE paper data collection tool is the preferred method to transmit this information to Novartis.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the AE data collection tool sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the investigator to complete and sign the AE data collection tool within the designated reporting timeframes.

10.1.2 Serious adverse events

An SAE is defined as any AE [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:

- fatal
- life-threatening

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

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

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

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

Any suspected transmission via a medicinal product of an infectious agent is also considered a SAE.

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 8 weeks after the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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.

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 CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same 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.

Any SAEs experienced after 8 weeks after the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

SAE Reporting via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to Novartis will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or by telephone.

SAE Reporting via Paper Data Collection Tool

Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to Novartis.

In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.

10.1.4 Pregnancy reporting

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

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment 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, participant 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.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant 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 16-1 in Section 16.2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 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 16-2.

- Repeat liver chemistry tests (i.e., ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation. These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF. If the

initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.

- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
- These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

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

10.2.2 Adjudication committee

The role of the Adjudication Committee (AC) is to ensure that all treatment outcomes are judged uniformly, using standard criteria and processes. The AC will be composed of clinical experts to evaluate disease progression and harmonize endpoint assessment criteria using data provided by the sponsor.

Specific details regarding endpoint definitions can be found in the adjudication charter.

MAS adjudication committee

An independent Adjudication Committee will review and adjudicate information on all potential cases of MAS as long as adjudication for potential MAS cases is required as an additional pharmacovigilance activity according to adjudication committee charter. Potential cases will be identified through systematic database search of specified AE terms and/or (abnormal) laboratory criteria specified by the MAS adjudication committee. The Committee will review cases as they are identified. A report of the adjudication outcome will be provided to the Sponsor. As part of the adjudication process, a request for supplemental data collection will be sent to the investigator (as needed). If biological specimens (e.g., bone marrow aspirate, bronchoalveolar lavage, etc.) were collected as part of customary diagnostic workup, samples, such as tissue slides, may be requested by the committee for their review and/or for specialized analysis such as immunohistochemical staining CCI

Participants and parents will provide written informed consent for providing additional specimens. The MAS Adjudication Committee Charter provides detail on the committee composition, adjudication process, database AE and laboratory criteria search terms, and supplemental data package. The outcome of the adjudication will be reported on the MAS Adjudication CRF. The MAS Adjudication Committee Charter is available upon request.

11 Data Collection and Database management

11.1 Data collection

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

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

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

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

11.2 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. Electronic Source (eSource) DDE or eCRFs) 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 field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each participant 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 participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary 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 participants will be disclosed.

12 Data analysis and statistical methods

The statistical analysis of this study will be performed by Novartis. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

The primary efficacy analysis will be based on the data up to the time when the first11 participants have completed Week 28. Summary statistics for continuous variables will generally include n, mean, standard deviation, median, minimum, and maximum. For categorical variables, this will generally include frequency and percentage. For selected parameters, 25th and 75th percentiles will also be presented when applicable. Further details of the statistical considerations will be provided in the statistical analysis plan (SAP).

12.1 Analysis sets

The Full Analysis Set (FAS) and Safety set comprise all participants who received at least one dose of study treatment.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for the FAS.

Relevant medical histories and current medical conditions at baseline will be summarized combined by system organ class and preferred term for the FAS.

12.3 Treatments

The duration of exposure in days to canakinumab treatment and the number of injections will be summarized by means of descriptive statistics using the safety set.

Prior and Concomitant medications will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system for the safety set. Significant non-drug therapies prior to and after the start of the study treatment will also be summarized.

12.4 Analysis supporting primary objectives

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary estimand is the response to treatment according to the adapted ACR 30 criteria at Week 8 excluding the effect of corticosteroid dose increase and/or intravenous administration of corticosteroid.

12.4.2 Statistical model, hypothesis, and method of analysis

The aim is to evaluate the treatment effect of canakinumab for Japanese AOSD participants on the adapted ACR 30 response at Week 8. The justification of the corresponding primary estimand are detailed in Section 2.1.

The primary objective will be achieved if the null hypothesis is rejected at the 2.5% one-sided level of significance.

$H_0: p_{ACZ} \leq 0.40$ vs. $H_A: p_{ACZ} > 0.40$,

with p_{ACZ} being the proportion of participants who achieved adapted ACR 30 at Week 8.

Frequency tables with the number and percentage of participants who achieved adapted ACR 30 response together with a 95% confidence interval will be provided based on the FAS. A binomial test using the normal approximation will be performed and the Wald asymptotic confidence interval with continuity correction will be presented.

12.4.3 Handling of intercurrent events of primary estimand

The primary analysis will account for different intercurrent events as explained in the following:

1. **Systemic corticosteroid dose increase and/or iv corticosteroid use before Week 8 for any reason**: If a participant had corticosteroid dose increase and or iv corticosteroid use during the first 8 weeks after study treatment start, he/she will be considered as non-responder (non-responder imputation).
2. **Discontinuation of study treatment before Week 8 for any reason**: If adapted ACR 30 assessment at Week 8 is available, it will be included in the analysis.

Further details about the intercurrent events are provided in Section 2.1.

12.4.4 Handling of missing values not related to intercurrent event

Missing adapted ACR 30 assessment at Week 8 will be imputed with non-responder regardless of the reason for missing data (non-responder imputation).

12.4.5 Supplementary analysis

The supplementary clinical question of interest is: What is the benefit of Canakinumab in Japanese AOSD patients to improve systemic and articular manifestation of AOSD regardless of systemic corticosteroid dose increase and/or intravenous administration of corticosteroid and regardless of treatment discontinuations for any reason? In this supplementary estimand, the population, primary variable and summary measure will be the same as the primary estimand, but the intercurrent event of corticosteroid dose increase and/or intravenous administration of corticosteroid will be ignored following a treatment policy strategy. The supplementary estimand will capture the effect of canakinumab regardless of increase in systemic corticosteroid dose and intravenous administration of corticosteroid, reflecting possibly the situation under clinical practice.

12.5 Analysis supporting secondary objectives

12.5.1 Key efficacy endpoint

The secondary estimand is the effect of canakinumab on oral corticosteroids tapering starting from Week 8 to Week 28. Successful tapering of corticosteroids will be derived on prednisone equivalent dose per day (mg/kg/day) as described in Section 8.3.2. Further details will be described in the statistical analysis plan.

Frequency table with the number and percentage of participants who were able to taper oral corticosteroids successfully at Week 28 will be provided for the FAS. The participants who used systemic corticosteroid at baseline and were administered study treatment at Week 8 will be considered in this analysis.

The analysis will account for different intercurrent events as explained in the following:

1. Discontinuation of study treatment after Week 8 for any reason: If a participant early discontinued study treatment after Week 8 but had the Week 28 assessment regarding corticosteroid tapering, he/she will be included in the analysis.
2. Intravenous administration of steroid at any time between Week 8 and Week 28: If a participant had intravenous administration of steroid at any time between Week 8 and Week 28, he/she will be considered as corticosteroid tapering failure (non-responder imputation)

If the successful tapering of corticosteroids cannot be derived due to missing body weight, it will be imputed with the last available data from Week 8 to Week 28 (last observation carried forward (LOCF) approach).

12.5.2 Efficacy and/or Pharmacodynamic endpoint(s)

All efficacy endpoints will be summarized using the FAS.

Adapted ACR 30/50/70/90/100 response criteria

Frequency tables with the number and percentage of participants achieving the adapted ACR 30/50/70/90/100 criteria will be provided by scheduled visit.

Components of adapted ACR criteria

For the ACR individual components, summary statistics for the observed values and the change/percent change from baseline will be provided by scheduled visit.

Corticosteroid dose tapering

For oral corticosteroid dose, summary statistics for the change/percent change from baseline will be provided by scheduled visit after Week 8.

Rash

Frequency table with the number and percentage of participants in absent/present and typical or/and atypical if present will be provided by scheduled visit. The details on rash assessment are described in Section 8.3.3.

DAS28-CRP

Summary statistics for the observed values and the change from baseline will be provided by scheduled visit.

Systemic feature score

For total score and, summary statistics for the observed values and the change from baseline will be provided by scheduled visit.

For each component score, the number and percentage of participants whose score is 1 will be provided by scheduled visit.

Total IL-1β level

Total IL-1β will be summarized by means of arithmetic and geometric mean, standard deviation (SD), coefficient of variation (CV) for arithmetic and geometric mean, median, minimum and maximum.

12.5.3 Safety endpoints

For all safety analyses, the Safety set will be used.

Adverse events

All information obtained on AEs will be displayed by participant.

The number and percentage of participants with treatment emergent AEs (events started after the first dose of study medication or events present prior to start of study treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by primary system organ class and preferred term.
- by primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related AEs, death, SAEs, other significant AEs leading to discontinuation.

The number and percentage of participants with AEs of special interest (AESI) will be summarized. AESI will be defined based on the latest Case Retrieval Strategy.

A participant with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by participant, and visit and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by scheduled visit.

ECG

All ECG data will be listed by participant and visit, abnormalities will be flagged. Summary statistics will be provided by scheduled visit.

Clinical laboratory evaluations

All laboratory data will be listed by participant and visit and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by scheduled visit. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Immunogenicity

All immunogenicity results will be listed by participant and visit.

12.5.4 Pharmacokinetics

Pharmacokinetic parameters will be listed by participant and visit. Descriptive summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum for the FAS.

12.6 Analysis of exploratory endpoints

12.6.1 CCI

CCI

CCI

12.6.2 CCI

CCI

12.6.3 CCI

CCI

12.7 Interim analyses

Two interim analyses will be performed after all participants have completed Week 28 to support the registration dossier, and Week 48 to supplement the dossier with long-term safety and efficacy data. At the interim analysis at Week 28, the primary efficacy analysis will be conducted based on the data up to the time when the first 11 participants have reached Week 28 (or prematurely discontinued prior to Week 28), as per PMDA feedback received in Feb 2023. A final analysis will be performed after all participants have completed the study.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

CCI

CCI

13 Ethical considerations and administrative procedures

13.1 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 GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. 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.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

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

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

14 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 participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety 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 participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

The following defined notable laboratory or vital sign abnormalities, except creatinine clearance, will be communicated at the same time as they are sent to investigators to Novartis. Novartis will determine if further consultations with Investigator(s) are appropriate.

Newly occurring selected notable laboratory abnormalities :

- Albumin: < LLN
- >3x-, 5x-, 8x-, and 10x-ULN elevations of AST, ALT, and either ALT or AST*
- Any elevations of bilirubin > ULN; elevated bilirubin to >1.5xULN, and to >2xULN*
- Any elevations of ALP >1.5xULN, >2xULN, >3xULN*
- Elevation of AST and/or ALT (>3xULN, >5x-, >10x) accompanied by elevated bilirubin (>2xULN)*
- ALT or AST >3x ULN and TBL >2x-, and ALP <2xULN
- ALP >3xULN and TBL >2xULN
- Gamma-Glutamyltransferase (GGT): > 3 x ULN
- Creatinine (serum): ≥ 1.5 x ULN
- Creatinine clearance (Cockroft-Gault formula): ≥ 25% decrease from baseline
- Creatinine clearance (Cockroft-Gault formula): ≥ 25% decrease from average baseline in two consecutive visits that are ≥ 14 days apart
- Potassium: ≥ 5.5 mmol/L, or ≤ 3.0 mmol/L
- Magnesium: ≥ 1.5 mmol/L, or ≤ 0.5 mmol/L
- Sodium: ≥ 150 mmol/L, or ≤ 130 mmol/L
- Calcium:≥ 1.2 x ULN or < Lower Limit of Normal (LLN)
- Hemoglobin: ≥2 g/dL decrease from baseline, or < 10.0 g/dL
- Platelet count: < LLN
- White blood cell count: ≤ 0.8 x LLN or ≥ 1.2 x ULN
- Neutrophils: ≤0.9 x LLN or ≥ 1.2 x ULN
- Eosinophils: ≥ 1.1 x ULN
- Lymphocytes: < LLN or ≥ 1.1 x ULN
- Protein urine dipstick: ≥ ++

Newly occurring selected notable vital signs abnormalities in adult patients :

- Systolic/Diastolic blood pressure: ≥25% decrease or ≥25 % increase from baseline or to ≥140/90.
- Pulse: ≥110 bpm with ≥15% change from baseline, or < 50 bpm with ≥15% change from baseline

* FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation

Note: Only post-baseline values will be flagged as notable abnormalities

Cockroft-Gault formula (Men): CrCl (mL/min) = [((140-age (years)) x weight (kg)) / (serum creatinine(µmol/L) / 88.4) (mg/dL) x 72]

Cockroft-Gault formula (Women): CrCl (mL/min) = [((140-age (years)) x weight (kg)) / (serum creatinine (µmol/L) / 88.4) (mg/dL) x 72] x 0.85

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	● ALT or AST > 5 × ULN ● ALP > 2 × ULN (in the absence of known bone pathology) ● Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) ● ALT or AST > 3 × ULN and INR > 1.5 ● Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) ● Any clinical event of jaundice (or equivalent term) ● ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia ● Any AE potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	● ALT or AST > 3x baseline or > 300 U/L (whichever occurs first)

Table 16-2 Follow up requirements for liver laboratory triggers – ALT, AST, TBL

ALT	**TBL**	**Liver Symptoms**	**Action**
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	● **No change to study treatment** ● Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. ● Follow-up for symptoms.
If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	● **Interrupt study drug** ● Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. ● Follow-up for symptoms. ● Initiate close monitoring and workup for competing etiologies. ● Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 16-3 Follow up requirements for liver laboratory triggers – Isolated hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	● Maintain treatment ● Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	● Interrupt treatment ● Repeat LFT within 48-72 hours ● Hospitalize if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	● Discontinue the study treatment immediately ● Hospitalize the participant ● Establish causality ● Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity	● Consider study treatment interruption or discontinuation ● Hospitalization if clinically appropriate ● Establish causality ● Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion

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Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.3 Appendix 3: Yamaguchi criteria

Major criteria

- Fever ≥ 39 °C lasting 1 week or more
- Arthralgia lasting 2 weeks or more
- Typical skin rash: maculopapular, nonpruritic, salmon-pink rash with concomitant fever spikes
- Leukocytosis ≥10,000/mm^3 with neutrophil polymorphonuclear proportion ≥ 80%

Minor criteria

- Pharyngitis or sore throat
- Lymphadenopathy and/or splenomegaly
- Liver enzyme abnormalities (aminotransferases)
- Negative for RF or antinuclear antibodies

Exclusion criteria

- Infection, especially sepsis and Epstein–Barr viral infection
- Malignant diseases, especially lymphomas
- Inflammatory disease, especially polyarteritis nodosa

Classification requirement

- At least five criteria, including two major criteria and no exclusion criteria