Study Protocol for a Multi-Centre, Placebo-Controlled Phase II Study of Canakinumab for the Treatment of Adult-onset Still's disease (AOSD) including an open-label long term extension.

Protocol No.: CACZ885GDE01T / NCT02204293

EudraCT No. 2011-001027-20

Protocol version: 3.1

Short name of the protocol: CONSIDER
(**C**anakinumab for treatment of adult **on**set **S**till's **d**isease to achi**e**ve **r**eduction of arthritic manifestation)

Date of the protocol: 20.10.2017

Principal Investigator:

Prof. Dr. med. [redacted]
[redacted]
Tel. [redacted]
Fax. [redacted]
E-mail: [redacted]

Protocol Synopsis

Title:	**A Multi-Centre, Placebo-Controlled Phase II Study of Canakinumab for the Treatment of Adult-Onset Still's Disease (AOSD)-core study, including an open-label long-term extension - LTE**
Acronym:	CONSIDER (**C**anakinumab for treatment of adult **on**set **S**ti**l**l's **d**isease to achi**e**ve **r**eduction of arthritic manifestation)
Study drug:	Canakinumab
Clinical phase:	II
Rationale:	Interleukin-1 antagonists such as canakinumab have been used for the treatment of AOSD and have had a marked influence on the activity of the disease, including joint mobility. Results from controlled clinical studies are not, however, currently available.
Objectives of the core study:	Primary objective: Investigation of the efficacy of canakinumab in patients with AOSD and active joint involvement in terms of the proportion of patients with a clinically-significant reduction in disease activity (Δ DAS28 > 1.2) following a treatment period of 12 weeks. Secondary objective: 1. Evaluation of the safety of canakinumab in patients with AOSD 2. Evaluation of the efficacy of canakinumab in patients with AOSD and joint involvement in terms of the ACR and EULAR Response Criteria for weeks 12 and 24 3. Proportion of patients achieving low disease activity (< 3.2) or remission (< 2.6) based on DAS28, 4. Recording of the change in joint mobility using the neutral zero method, 5. Investigation of the general changes in health based on HAQ-DI and SF-36, 6. Improvement in the skin manifestation of AOSD and the frequency of fever, 7. Reduction in inflammatory markers (CRP, ESR, ferritin), 8. Biomarker analysis (mRNA, protein) aimed at identifying predictive biomarkers (for those participating in the accompanying project).
Objectives of the long-term extension part:	Primary objective: Evaluation of the long-term safety of canakinumab in patients with AOSD and articular involvement Secondary objectives: 1. Description of the long-term efficacy of canakinumab in patients with AOSD according to EULAR response criteria (proportion of patients showing prolonged clinically improvement according to DAS28 low-disease activity [< 3.2] and remission [< 2.6], reduction of flares and glucocorticoid intake). 2. Assessment of health outcome measures (HAQ-DI, SF36), improvement in skin manifestation and reduction of inflammatory markers of disease under long-term treatment. 3. Evaluation if a reduced dosage of canakinumab can be used to control disease activity by down-titration from 4mg/kg/body weight (BW) (max 300mg)/month to 2mg/kg/BW (max 150mg)/month
Design	Core study: double blind, placebo-controlled LTE: open-label
Number of patients:	68 (Core phase); 35 (LTE phase)

Number of study centres:	Approx. 14 study centres in Germany
Duration of study treatment:	Core study: 6m LTE: 24 m
Duration of participation in the study:	Screening: up to 4 weeks Study treatment duration (see above) Follow-Up: up to 3 months
Inclusion criteria:	1. Written and signed consent from the patient to participate in the study 2. Men and women aged ≥ 18 years and ≤ 75 years 3. Fulfilment of AOSD classification criteria (according to Yamaguchi et al, J. Rheumatology, 1992) 4. Disease activity based on DAS28 of ≥ 3.2 at screening 5. At least 4 painful and 4 swollen joints at screening and baseline (of the 28 joints according to DAS28) 6. If undergoing treatment with NSAIDs, stable dose for at least 2 weeks prior to randomisation 7. If undergoing treatment with glucocorticoids, stable dose of ≤10 mg/day (prednisolone or equivalent) for at least 1 week prior to randomisation 8. If undergoing treatment with conventional DMARD, stable dose for at least 6 weeks prior to randomisation 9. Normalisation period for biological DMARDS (anakinra 1 week, etanercept 2 weeks, adalimumab, certolizumab, abatacept s. c. and tocilizumab s. c. 1 month, infliximab, golimumab, abatacept and tocilizumab (i.v.) 3 months, canakinumab 6 months, rituximab 9 months) prior to randomisation 10. In patients of reproductive age, use of an effective method of contraception as well as negative pregnancy test prior to the study commencing.
Exclusion criteria:	1. Previous treatment with the study drug with repeated administration of canakinumab 2. Intraarticular or intravenous administration of glucocorticoids within 4 weeks prior to the baseline or use of narcotic analgesics except for analgesics permitted within the framework of the investigation (codeine and tramadol) 3. Presence of another, serious chronic-inflammatory disease 4. Positive hepatitis B antigen (HBsAg), hepatitis C antibodies and/or HIV antibodies. 5. Presence of a relevant, active infection or other diseases, which entail a tendency towards infection. 6. Positive screening for latent tuberculosis, in accordance with usual local practice. If patient is taking adequate/isoniazid prophylaxis for 4 weeks before first IP administration, this patient may be randomized. 7. Raised liver count (raised bilirubin; ALT or AST ≥3-fold the normal range) 8. Serum-creatinine concentration >1.5 mg/dl 9. Inadequate haematological findings (Hb ≤ 9 g/dl, neutrophils ≤ 2,500/µl and thrombocytes ≤ 100,000/µl) 10. Simultaneous participation in any other interventional clinical study within the last 30 days preceding the commencement of the study 11. History of neoplasia with the exception of a curatively treated non-melanoma skin tumour or carcinoma of the cervix treated in situ without any indication of recurrence within the last 10 years

	12. Relevant cardiac or pulmonary disorders 13. Severe intercurrent neurological or psychiatric disorders 14. Macrophage activation syndrome (MAS) as part of previous treatment with IL-1 blockade (e.g. anakinra, rilonacept) 15. Vaccination with a live vaccine within 3 months before the baseline 16. A history of alcohol or drug abuse in the past 12 months 17. ≥400 ml donation or loss of blood up to 8 weeks before the baseline 18. Pregnancy or breast-feeding 19. Commitment of the patient to an institution at the direction of an authority or court
Classification criteria for entering the LTE:	1. Participation in the randomized, placebo-controlled trial (CACZ885GDE01T) (core study) 2. Considered to be a responder with respect to articular involvement (Δ DAS28 > 1.2) as well as to systemic disease manifestation of AOSD at week 24 3. In case of female patient of childbearing potential, she agrees to comply with effective contraceptive measures, has been using contraception since the last menses, will use adequate contraception during the study and has a negative test at week 24
Dosage and administration of the study drug	In the active treatment arm (n=34), the drug being investigated, canakinumab, will be administered while the control group (n= 34) will receive placebo injections. The study drug and the placebo will be administered subcutaneously. Canakinumab will be administered subcutaneously in a dose of 4mg/kg body weight up to a maximum of 300 mg every 4 weeks. No escalation in dosage is envisaged. A re-evaluation will take place in week 12. It is expected that at this point in time, approx. 75% of patients will change over from the placebo to the verum group, if no significant improvement has been achieved according to DAS28 (a significant improvement is defined as an improvement in DAS28 from visit 2 to visit 5 of > 1.2).
Investigations regarding the safety of the treatment	1. Blood count, Na, K, creatinine, ALT, AST, GGT, AP, LDH, ferritin and urine test sticks at each visit 2. Recording of adverse events over the entire period 3. Recording of vital signs and physical examination at each visit
Pharmacokinetics (PK):	The serum-canakinumab concentration will be established at all visits from the baseline, in episodes of illness and in the event of a macrophage activation syndrome (MAS) occurring. In the event of an anaphylactic reaction, samples will be investigated following the injection and at intervals of 8 weeks.
Pharmacodynamics (PD):	Overall IL-1ß (circulating IL-1ß as well as connected to canakinumab) will be investigated at all visits.
Analysis of efficacy:	Primary endpoint: clinically relevant reduction in DAS28 (>1.2 units) between baseline (mean DAS28 of visit 1 and visit 2) and week 12 (double blind period). Secondary endpoint parameters: Joint manifestation: 1. DAS28 (Disease activity score) 2. ACR (American College of Rheumatology) Response Criteria and EULAR response criteria for low disease activity (DAS28 < 3.2) and remission (DAS28 < 2,6) Assessment of the level of disability and of quality of life 1. Health Assessment Questionnaire Disability Index (HAQ-DI)

	2. SF-36 health survey Laboratory tests 1. Serological markers for inflammatory reactions (CRP, ESR, ferritin) 2. Immunogenity (anti-canakinumab antibodies) will be established at all visits, in the case of episodes of illness and with MAS. In the event of an anaphylactic reaction occurring, samples will be investigated following the injection and at intervals of 8 weeks. Additional investigations Optional scientific accompanying project on biomarker analysis: 1. Soluble serum protein in connection with pathomechanism investigated such as IL-6 and IL-18, S100 as an inflammatory marker; 2. Pharmacogenomic investigations with mRNA profile in connection with investigated pathomechanism for the stratification of patients with regard to responsiveness to treatment; 3. Investigations into mRNA expression in connection with macrophage activation syndrome for Perforin-, SOCS3-, MUNC 12-4; 4. Pharmacogenetic investigations into identifying Single Nucleotide Polymorphisms [SNP], as well as sequencing of the genome for the stratification of patients with regard to responsiveness to treatment.
Statistical evaluation:	The statistical evaluation of the safety and efficacy of canakinumab will be conducted according to the Intention-to-treat principle. Patients who have terminated the study early will be counted as non-responders. The DAS28 response rates to week 12 (primary endpoint) will be compared by means of Fisher's exact test. This test will also be used to compare secondary binary endpoints. The comparison of mean values will be made using the t-tests and Mann-Whitney test. 95% confidence intervals will be stated for all response rates and safety signals.
Ethical aspects:	The study will be carried out in accordance with currently valid legal provisions, including the Guidelines on Good Clinical Practice (GCP) and the ethical principles of the Helsinki Declaration.

Study Procedures

Procedures	Visit 1 Screening (-1 week to -4 weeks)	Visit 2 baseline (Day 0)	Visit BM with accompanying project (Day 7-10)	Visit 3 Week 4 (+/- 3 days)	Visit 4 Week 8 (+/- 3 days)	Visit 5 Week 12 (+/- 3 days) (switch [2])	Visit 6 Week 16 (+/- 3 days)	Visit 7 Week 20 (+/- 3 days)	V8 Week 24 (+/- 3 days) *[8]	End of core study [(7)] Wk 28/Wk 40 (+/- 3 days)
Informed consent	X	X [(1)]								
Demographic data	X									
Medical history	X									
Physical examination	X	X		X	X	X	X	X	X	X
Vital signs	X	X		X	X	X	X	X	X	X
Concomitant medication	X	X		X	X	X	X	X	X	X
Inclusion or exclusion criteria	X	X								
Adverse events		X	X	X	X	X	X	X	X	X
Differential blood count	X	X		X	X	X	X	X	X	X
Electrolytes (Na, K)	X	X		X	X	X	X	X	X	X
Creatine, ALT, AST, GGT, AP, LDH, ferritin	X	X		X	X	X	X	X	X	X
CRP	X	X		X	X	X	X	X	X	
ESR	X	X		X	X	X	X	X	X	
Electrophoresis protein	X									
Pregnancy test	X									
Anti-canakinumab antibodies [6]		X		X	X	X	X	X	X	X
ANA	X					X			X	X
HIV, Hepatitis B and C serology	X									
Urine test sticks	X	X		X	X	X	X	X	X	X
ECG		X								X
Tuberculosis screening [3]	X									
Joint status (28)	X									
Joint status (68/66)		X		X	X	X	X	X	X	
Joint mobility [4]		X				X			X	
PGA	X	X		X	X	X	X	X	X	
PhGA	X	X		X	X	X	X	X	X	
HAQ-DI		X				X			X	
SF-36		X				X			X	
Administration of the study drug [5]		X		X	X	X [(2)]	X [(2)]	X [(2)]		
Pharmacodynamics		X		X	X	X	X	X	X	
Pharmacokinetic properties [6]		X		X	X	X	X	X	X	
Optional biomarker study [1]		X	X	X						
LTE [8]									X [(8)]	

1. Additional informed consent required for the accompanying project. In the event of an episode of illness or MAS or suspected MAS.

2. Responders (ΔDAS28 > 1.2) remain under masked treatment until week 40, final injection at week 20.
Unblinding of the non-responders: non-responders in the placebo group receive canakinumab 4mg/kg body weight (max. 300 mg) subcutaneously openly at weeks 12, 16 and 20.
non-responders in the verum group remain without the study drug in the safety follow-up until week 28.

NR: non-responder

3. Chest X-ray within the last 3 months + PPD test and /or Quantiferon test

4. Neutral zero method

5. Subcutaneous injections of canakinumab / placebo are prepared, applied and recorded by an independent drug administrator.
This member of staff is not permitted to carry out any further study-specific actions within the framework of this study.

6. Is established at all visits from baseline, in the event of episodes of illness or MAS, or suspected MAS. In the event of an anaphylactic reaction occurring, samples will be investigated following the injection and at intervals of 8 weeks.

7. for patients not classifying for LTE

8. please refer to LTE-flow-chart, page 8 and study procedures graphic at page 10

In the event of premature discontinuation or termination of the study by a decision of the sponsor, the investigating doctor or the study participant, the visit will be carried out in week 24. Furthermore, a concluding visit will take place while recording the adverse events with an interval of 20 weeks after the last administration of the study drug.

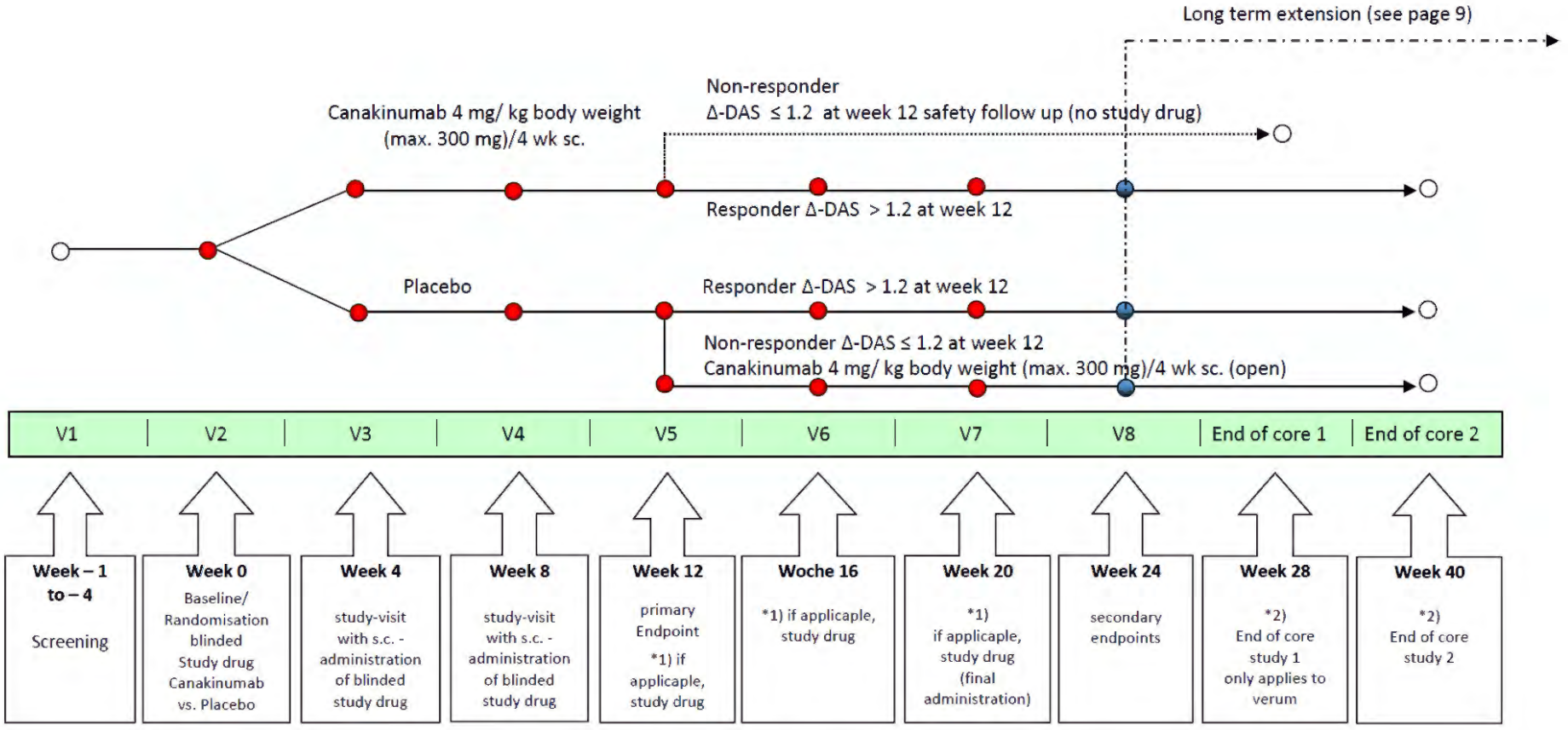
Study Procedures-LTE

Procedures	Visit 8 Week 24 (end of core study treatment) Entry in LTE	Visits 9 – 31 Week 28/ Month 7 – 30 (+/- 1 week)	V 32/EOS Month 33
Classification criteria for LTE	X		
Physical examination	X	X	X
Vital signs	X	X	X
Concomitant medication	X	X	X
Adverse events	X	X	X
Differential blood count	X	X	X
Electrolytes (Na, K)	X	X	X
Creatine, ALT, AST, GGT, AP, LDH	X	X	X
Ferritin	X	X	X
CRP	X	X	X
ESR	X	X	X
Electrophoresis protein	X		X
Pregnancy test	X		
Anti-canakinumab antibodies [6]	X	X	X
ANA	X	X	X
Urine test sticks	X	X	X
ECG	X		X
Joint status (28)	X	X	
Joint status (68/66) [9]	X	X [9]	
Joint mobility [9]	X	X [9]	
PGA	X	X	
PhGA	X	X	
Evaluation of down-titration criteria [10]		X [10]	
HAQ-DI [9]	X	X [9]	
SF-36 [9]	X	X [9]	
Administration of canakinumab	X	X	
Pharmacodynamics	X	X	
Pharmacokinetic properties [6]	X	X	
Optional biomarker study [1]	X		

9. 66/68 joint count, joint mobility, HAQ-DI and SF-36 to be performed quarterly

10. down-titration from 4 mg/kg/body weight (BW) (max 300 mg)/month to 2 mg/kg/BW (max 150 mg)/month in case of remission defined as a DAS28 < 2.6 AND no signs of systemic disease activity at two consecutive (monthly) visits, after (and including) visit 9 (week 28).
In case of increasing disease activity or flare under a reduced dosage of canakinumab, up-titration to the initial dosage is possible (for details refer to 3.9).

CONSIDER - Core Study procedures

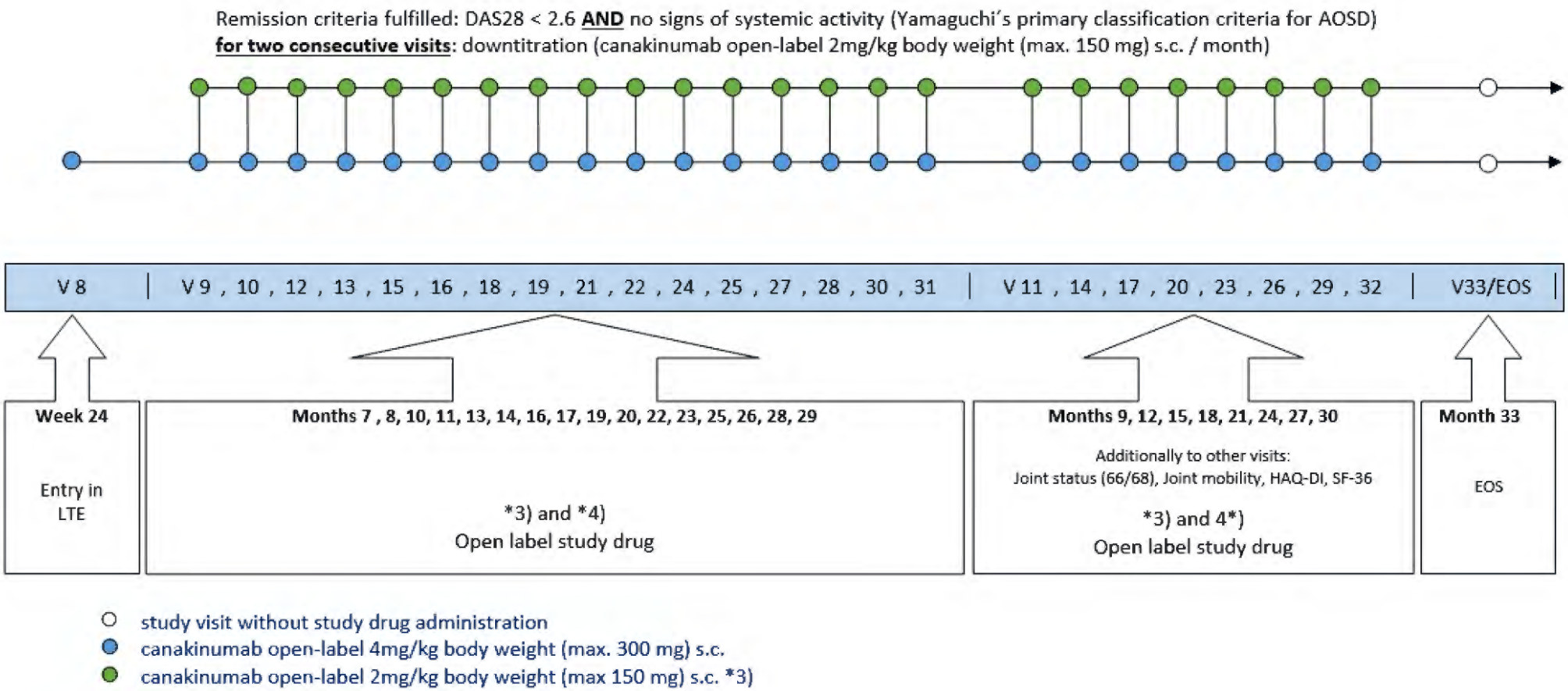


*1) responder (Δ DAS28 > 1.2) remains under masked treatment until week 40. Final injection at week 20.
Unblinding of the Non-Responder: non-Responder in the placebo group receive canakinumab 4 mg/kg body weight (max. 300 mg) s.c. openly at weeks 12, 16 and 20.
non-Responder in the verum group stay receive no study drug and have a safety follow-up until week 28.

*2) for patients not classifying for long term extension

- study visit without study drug administration
- study visit with study drug administration
- long term extension

CONSIDER - LTE Study procedures



* 3) If remission criteria fulfilled: DAS28 < 2.6 **AND** no signs of systemic activity (Yamaguchi´s primary classification criteria for AOSD) **for two consecutive visits** consider down-titration: canakinumab open-label 2mg/kg body weight (max 150 mg) s.c. / month

*4) In case of flare (see 3.9) under a reduced dosage of canakinumab, up-titration to the initial dosage is possible.

One application at most can be missed during the study.

Table of Contents

1. Introduction and rationale of the clinical study

1.1. Overview of the clinical picture

Adult onset Still's disease (AOSD) is a rare systemic inflammatory disease. The cause of the disorder is unknown. The clinical picture is characterised by periodic fever attacks, usually accompanied by a passing, salmon-coloured rash and polyarthritis (1, 2, 3). The clinical picture of AOSD occurs in a similar form in systemic juvenile arthritis (JIA). The occurrence of fever has been described in about 95.7% of cases in retrospective studies (1, 4, 5) and in most cases precedes the other manifestations of the disease. The recurrent fever attacks typically occur once or twice a day, with the highest temperatures occurring late in the afternoon.
The typical macular or maculopapular rash which usually accompanies the reaction to fever, especially in the evening and at night, is fleeting and salmon pink in colour (5, 6). The rash is described in approx. 73% of patients and predominantly occurs in the thigh and trunk area. Pruritus is sometimes reported (32% of patients in a Dutch cohort), meaning that it could be confused with an allergic reaction to medication (1, 7, 8). Histological findings often reveal a discrete perivascular inflammation on the upper dermis with infiltrates of lymphocytes and histiocytes (9).

The mortality of the disease may have fallen in the last few years. While it was stated as still being at 10% up to 1990 within a period of 12 years (6, 10, 11, 12), a meta-analysis of 5 studies published in 2008 reveals mortality of 4% within a period of 5 to 13 years (13). The most frequent causes of death within this are usually stated as being sepsis, hepatic failure and haemophagocytic syndrome (or macrophage activation syndrome, MAS). The prognosis for AOSD primarily depends on the visceral participation of organs (7, 8, 14), with a secondary amyloidosis (type AA), which considerably increases mortality. The secondary amyloidosis frequently occurs with the progress of refractory AOSD stretching over a number of years, in which the participation of the kidneys in particular plays a key prognostic role (15, 16, 17).

The cause of AOSD is still unexplained. Possible trigger factors are assumed to be infectious diseases caused by viruses and bacteria, but no active infectious disease can usually be established in terms of disease manifestations (9, 11). A genetic association with the features of HLA (B17, B18, B35, DR2) have been described in some studies (7, 9, 14, 18). The inflammatory reaction is mediated in the pathogenesis through the raised secretion of various cytokines, with raised serum levels of IL-1, IL-6, TNF-a and IL-18 in particular being measured in highly active AOSD patients (7, 8, 9, 14, 18).

Epidemiological data regarding the incidence and prevalence of the disease are only insufficiently available. The disease occurs worldwide, with females appearing to be somewhat more frequently affected. AOSD usually affects young people with the age of first manifestation being between 16 and 35 years old in 75% of cases (7, 8). Prevalence was stated in 1990 as being at 0.16 to 3.4/100,000 and in 2000 at 6.9/100,000 (19, 20). The annual incidence in Norway was stated as being 0.4/100,000 (20).

The treatment available until now has consisted in particular of measures targeted at the symptoms using non-steroid anti-inflammatory drugs (NSAIDs). In the case of pronounced systemic disease manifestation, immunosuppressive drugs such as glucocorticoids and disease modifying anti-rheumatic drugs (DMARDs) are also used. In cases of progress where there is resistance to therapy, biologicals have likewise been increasingly used, with good

results in particular for Interleukin-1 inhibitors having been published in case descriptions as well as in small cohort studies. In various case series, the achievement of remission of the disease could also be demonstrated. Furthermore, in one study, long-term remission from AOSD could also be shown in response to IL-1 blockade amongst patients who had previously had a high need for glucocorticoids and who had not responded to any other immunosuppressive drugs (DMARDs- and/or TNF blockers) (7, 8, 9, 14, 22). Amongst these patients, in addition to good clinical efficacy, a reduction in the glucocorticoid dose could also be achieved. Good tolerance of the treatment could be established overall. This provides good indications for an IL-1 blockade having good efficacy amongst patients with refractory AOSD (23, 24, 25, 26, 27).

Still's disease, as juvenile and adult manifestation, is considered to represent a disease continuum. This view is supported by a similar clinical presentation, the involved pro-inflammatory cytokine signature and known treatment effects under IL-1 inhibitors. In this context, canakinumab has shown strong efficacy and beneficial safety profile for treatment of systemic juvenile idiopathic arthritis (SJIA or juvenile Still's disease). The first controlled clinical trial of canakinumab in AOSD is performed to confirm these results in an adult population over a period of 24 weeks. First analyses of mRNA expression profiles, derived from these patients at baseline, revealed an upregulation of genes in AOSD which where responsive to successful canakinumab treatment in SJIA.

To provide long-term data on safety and efficacy, we aim to perform an extended treatment period until possible approval of the drug for this indication. Since it is of interest to clarify, whether this promising approach for treatment of SJIA as well as AOSD does require the same dose regimen, we also include the option for down-titration regimen in case of disease remission. Taken together, the aim of this long-term extension ~~of our~~ IIT in AOSD, is to investigate, whether canakinumab can be used with maintained efficacy and beneficial safety profile in AOSD patients.

Canakinumab is a specific IL-1ß-blocker with a good efficacy and safety profile in clinical applications to date with periodic fever syndromes in infantile- and adult-aged patients. Compared to other IL-1 blockers, fewer localised skin reactions in particular were observed with canakinumab. Canakinumab is approved for treatment in patients suffering from cryopyrin-associated periodic syndromes (CAPS) in Europe and the USA. This range of hereditary autoinflammatory syndromes is similar to AOSD, characterised by fever, skin rashes and an increase in inflammatory markers (28, 29, 30). The aim of this controlled clinical study in this process is to investigate the efficacy and safety of canakinumab amongst patients with active AOSD.

1.2. Canakinumab (Ilaris®)

1.2.1 Scientific background

Canakinumab (Ilaris®) is a pharmaceutical product of the class of active substances of immunosuppressives and is a human monoclonal anti-human-interleukin-1-beta-(IL-1-beta-) antibody of the IgG1/κ-isotype. Canakinumab attaches specifically to human IL-1 beta with high affinity and neutralises the biological activity of human IL-1 beta by inhibiting the interaction of this with IL-1 receptors, which means that the gene activation and formation of inflammatory mediators induced by IL-1 beta is prevented (32).

In clinical studies, CAPS patients responded rapidly to treatment with canakinumab, with pathological laboratory parameters, such as raised C-reactive protein (CRP), serum amyloid A (SAA), neutrophils and thrombocytes as well as leukocytosis, being normalised (32).

1.2.2 Pharmacology

The efficacy and safety of canakinumab have been proven amongst CAPS patients with varying degrees of severity of the disease and varying CAPS phenotypes. The approval of the drug under the trade name Ilaris has been secured for the treatment of adults, adolescents and children from the age of 4 with body weight exceeding 15 kg for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including:
1. Muckle-Wells Syndrome (MWS),
2. Multi-systemic inflammatory disease commencing at neonate age (Neonatal Onset Multisystem Inflammatory Disease; NOMID) or chronic infantile neuro-dermo articular syndrome (Chronic Infantile Neurological, Cutaneous, Articular Syndrome; CINCA),
3. Severe forms of Familial Cold Autoinflammatory Syndrome; FCAS)/Familial Cold Urticaria; FCU with indications and symptoms which go beyond a cold-induced urticarial skin rash (31).
The recommended dose of canakinumab amounts to 150 mg for CAPS patients with a body weight >40 kg or 2 mg/kg for CAPS patients with a body weight ≥15 kg and ≥40 kg. This dose is to be administered every eight weeks as a single dose in the form of a subcutaneous injection. If no clinically satisfying response (complete receding of the skin rash and other general inflammatory symptoms) has been achieved 7 days after the initiation of treatment, a second administration of 150 mg or 2 mg/kg canakinumab can be considered. If complete responsiveness to the treatment has then been achieved, the intensified dosage regime of 300 mg or 4 mg/kg should be maintained. No experience is available in the use of canakinumab at doses > 600 mg every 8 weeks. Clinical experience is limited in dosage intervals of less than 4 weeks (32).

Within the framework of the examination of canakinumab in studies involving systemic juvenile arthritis (JIA, Still's Disease), a dosage of 4 mg/kg subcutaneously every 4 weeks has been established to be the optimum dosage.

1.2.3 Toxicology

The most frequent side effects of treatment with canakinumab among patients with CAPS have been described as injection site reactions (20%), nausea, headaches, dizziness (11%), weight gain, muscle pains (10%), changes in blood count, liver count increases, as well as an increased risk of suffering slight and severe infections (nasopharyngitis, urinary tract infection, infection of the upper airways, viral infection) (30, 31).

1.2.4 Clinical pharmacokinetics and pharmacodynamics

In clinical studies, CAPS patients usually already respond to treatment with canakinumab after the first dose has been administered (28). Among adult CAPS patients, the peak concentrations of canakinumab in the serum (C_{max}) occurred approximately 7 days after a one-off subcutaneous administration of 150 mg. The average terminal half-life period stood at 26 days. On the basis of a pharmacokinetic analysis, the absolute bioavailability of subcutaneous canakinumab was estimated at 70%. The clearance (CL) and the distribution volume (V_{ss}) of canakinumab turned out differently depending on body weight and have been

estimated for a typical CAPS patient with a body weight of 70kg at 0.174 l/day or 6.01 litres. The accumulation ratio to be expected amounted after a subcutaneous administration of 150 mg canakinumab every 8 weeks to 1.3-fold. The exposition parameters (such as AUC and C_{max}) rose proportionately to the dose within a dosage range of 0.30 to 10.0 mg/kg as an intravenous infusion or from 150 to 300 mg as a subcutaneous injection. After repeated application, there were no indications of any accelerated clearance or changes in the pharmacokinetic properties of canakinumab depending on time. Following correction for body weight, no gender- or age-specific pharmacokinetic differences could be observed (32).

1.2.5 Clinical experience

Canakinumab is approved for the treatment of adults, adolescents and children from the age of 4 with body weight exceeding 15kg with Cryopyrin-Associated Periodic Syndromes (CAPS), gout arthritis and systemic juvenile idiopathic arthritis (31, 32). Canakinumab is being investigated in clinical studies in patients with juvenile idiopathic arthritis (JIA, Still's disease) as well as gout. Case reports have been published regarding treatment for Schnitzler's syndrome, Behcet disease, relapsing polychondritis, Sweet's syndrome, type 2 diabetes and AOSD (31).
NSAIDs, glucocorticoids and DMARDs (such as MTX, azathioprine, Cyclosporine A or cyclophosphamide) are usually administered in the treatment of AOSD. In the case of refractory forms of AOSD, biologicals (such as infliximab, adalimumab, etanercept, rituximab or tocilizumab) have been used with varying success in individual cases. Predominantly good treatment effects and persisting remission have been observed with the anakinra IL-1 blocker (23, 24, 25, 26, 27).

1.2.6 Potential risk factors

The use of canakinumab can be linked to increased occurrence of infections and serious infections (32). Patients should therefore be carefully monitored during and after treatment with canakinumab for any indications and symptoms of infections. Prior to initiating any treatment with a biological, it is recommended to boost the vaccination status, including pneumococci and influenza vaccinations. In about 12% of CAPS patients undergoing a PPD test (tuberculin skin test) in clinical studies, a positive test result was obtained in response to treatment with canakinumab during the follow-ups, without any indications of latent or active tuberculosis (32).
Further potential risk factors in response to the use of canakinumab can include changes in blood counts, including neutropenia. Increases in liver enzyme values while undergoing treatment are also possible (28). The risk of developing malignant diseases in connection with anti-interleukin (IL-) 1 therapy is unknown, but a potential risk cannot definitely be excluded (32).
Treatment with an IL-1 inhibitor such as canakinumab can lead to an increased expression of cytochrome P450. Patients undergoing co-medication with other drugs metabolised through the cytochrome P450 and with a narrow therapeutic range should therefore be monitored in terms of efficacy or the concentration of active substances (some antiepileptics, antimycotics, antidepressives, Leflunomide, Warfarin, etc.) (32).
There is limited literature available regarding reproduction toxicity and fertility. The use of effective contraception methods is therefore recommended during any treatment with Ilaris and for up to three months before commencing any such treatment (32).
The ability to drive can be impaired through potential side-effects such as light-headedness (31).

1.3. Rationale for the study and choice of drug dosage

No approved treatment options are currently available for the treatment of musculoskeletal manifestations with AOSD which have not responded to NSAIDs, glucocorticoids and DMARDs. Based on the good therapeutic effects which have been published with persisting remission reported in response to the IL-1 blocker anakrinra in cases of AOSD therapy resistance, this therapeutic approach is very promising. As, however, using the daily subcutaneous application of anakrina required is frequently accompanied by local reactions at the injection site, treatment with canakinumab promises to provide a sensible alternative due to a considerably longer application interval and fewer local reactions (32).
Canakinumab is an anti-IL-1-beta antibody with proven efficacy and a good safety profile with auto-inflammatory syndromes and is approved for the treatment of CAPS patients (32). This human, monoclonal antibody therefore appears to be suitable for the treatment of AOSD and is to be investigated within the framework of this study.

Within the framework of the examination of canakinumab in studies involving systemic juvenile arthritis (SJIA, Still's Disease), a dosage of 4 mg/kg body weight subcutaneously every 4 weeks has been established to be the optimum dosage. In the present study protocol for the treatment of AOSD, a dosage adjustment of canakinumab 4 mg/kg body weight up to a maximum dosage of 300 mg subcutaneously is envisaged, which is to be carried out every 4 weeks. The dose of canakinumab used in the process will continue to exceed the dose approved for the treatment of CAPS patients. As justification for the selection of the higher canakinumab dose, reference is made to the similarity of the clinical pictures of Still's disease in juvenile and adult age groups, while CAPS and Still's disease differ in clinical and pathogenetic terms. For this reason, an identical treatment dose as for Still's disease cannot definitely be inferred from proceeding from a dose of canakinumab known to be effective with CAPS. According to current knowledge gained from pharmacokinetic investigations, a higher dose with canakinumab is required in patients with SIJA compared to juvenile and adult CAPS patients. These data (33, 34) accepted for publication revealed that a dosage of canakinumab at 4 mg/kg body weight at an interval of four weeks was required in order to achieve a therapeutically effective plasma concentration of canakinumab.

The data available from the phase II clinical studies on the use of canakinumab (study A2203) with a dose of 4 mg/kg body weight at an interval of 4 weeks among patients with SIJA provide a basis for a dosage adjustment with regard to age (1-19 years). Furthermore, there are no indications of any excessive over- or under-dosing in the AUC vs. age analysis. It can therefore be assumed that a higher dose of canakinumab needs to be selected for the treatment of AOSD than for CAPS, based on the efficacy shown with SIJA. A relevant accumulation of canakinumab is not to be expected in this process due to the dosage corresponding to body weight and the limitation of the maximum dose.

2. Objectives of the study

2.1. Primary endpoint of the core study

- Investigation of the efficacy of canakinumab in patients with AOSD and active joint involvement. Primary endpoint: clinically relevant reduction in DAS28 of more than 1.2 between baseline (mean DAS28 of visit 1 and visit 2) and week 12 (double blind treatment period of 12 weeks).

2.2. Secondary objective parameters of the core study

- Evaluation of the safety of canakinumab in patients with AOSD
- Evaluation of the efficacy of canakinumab in patients with AOSD and joint involvement according to ACR and EULAR response criteria at weeks 12 and 24
- Improvement in skin manifestations, the frequency of fever and reduction in the inflammatory markers of the disease
- Proportion of patients achieving low disease activity (< 3.2) or remission (< 2.6) according to DAS28
- Investigation of general changes in health based on HAQ-DI and SF-36
- Recording of the change in joint mobility based on the neutral zero method

2.3. Primary objective parameters of the long term extension study

- Evaluation of the long-term safety of canakinumab in patients with AOSD and articular involvement

2.4. Secondary objective parameters of the long term extension study

- Description of the long term efficacy of canakinumab in patients with AOSD according to EULAR response criteria (proportion of patients showing prolonged clinically improvement according to DAS28 low-disease activity [< 3.2] and remission [< 2.6], reduction of flares and glucocorticoid intake)
- Assessment of health outcome measures (HAQ-DI, SF-36), improvement in skin manifestation, the frequency of fever and reduction of inflammatory markers of disease under long-term treatment.
- Evaluation if a reduced dosage of canakinumab can be used to control disease activity by down-titration from 4mg/kg/body weight (BW) (max 300mg)/month to 2mg/kg/BW (max 150mg)/month.

3. Study plan

3.1. General design and plan of the study

Patient population
Patients with AOSD and active joint manifestation are included in the study.

Centres and number of patients participating:
The study will be carried out at approx. 14 different centres under the supervision of the Department for Rheumatology and Clinical Immunology of the Charité. The inclusion of 68 patients with AOSD is envisaged.

Study design and methodology
Multi-centre, randomised, double blind, place-controlled phase II study for patients with AOSD and active joint involvement in response to stable symptomatic treatment with NSAIDs and DMARD. Having undergone previous treatment with biologicals is permitted, with attention being paid to the respective normalisation times prior to the conclusion of the study. Having undergone treatment with the study drug through the repeated administration of canakinumab represents a criterion for exclusion. In the event of canakinumab having been administered on a one-off basis, inclusion is possible based on the placebo-controlled study design, if the interval amounts to more than 6 months.
During the masked study phase, patients receive canakinumab at 4mg/kg body weight (up to a maximum of 300 mg subcutaneously vs. placebo subcutaneously) as study medication at baseline, in weeks 4 and 8. In the event of a response being obtained, further administration of the study medication of canakinumab 4mg/kg body weight up to a maximum of 300 mg subcutaneously vs. placebo subcutaneously is to be carried out at weeks 12, 16 and 20.
Non-responders will be unblinded at week 12. For patients in the placebo group showing no significant change in disease activity at week 12, an open administration of canakinumab 4mg/kg body weight up to a maximum of 300 mg will be carried out subcutaneously at week 12 as well as at weeks 16 and 20. Non-responders at week 12 from the canakinumab arm will not undergo further treatment with the study drug.

Long term extension
Patients who enter long-term extension:
A down-titration from 4mg/kg/BW (max. 300mg)/month to 2mg/kg/BW (max 150mg)/month can be considered after week 28 (visit 9) if the patient fulfils remission criteria defined as: a DAS28 < 2.6 AND no signs of systemic activity (Yamaguchi´s primary classification criteria for AOSD) for two consecutive visits.
In case of increasing disease activity or flare (see 3.9) under a reduced dosage of canakinumab, up-titration to the initial dosage is possible.

3.2. Selection of patients (Core)

3.2.1. Inclusion criteria

1. Written and signed consent from the patient to participate in the study
2. Men and women aged ≥ 18 years and ≤ 75 years
3. Fulfilment of the classification criteria of AOSD (according to Yamaguchi et al, J. Rheumatology, 1992)
4. Disease activity according to DAS28 of ≥ 3.2 at screening
5. At least 4 painful and 4 swollen joints at screening and baseline (of the 28 joints according to DAS28)
6. If undergoing treatment with NSAIDs, stable dose for at least 2 weeks prior to randomisation
7. If undergoing treatment with glucocorticoids, stable dose of ≤ 10 mg/day (prednisone or equivalent) for at least 1 week prior to randomisation
8. If undergoing treatment with conventional DMARD, stable dose for at least 6 weeks prior to randomisation
9. Normalisation period for biological DMARDS (anakinra 1 week, etanercept 2 weeks, adalimumab, tocilizumab s.c. and certolizumab 1 month, infliximab, golimumab, abatacept (i. v.) and tociluzumab (i.v.) 3 months, rituximab 9 months, canakinumab 6 months) prior to randomisation
10. In patients of reproductive age, use of an effective method of contraception as well as negative pregnancy test prior to the study commencing.

3.2.2. Exclusion criteria

1. Previous treatment with the study drug with repeated administration of canakinumab
2. Intraarticular or intravenous administration of glucocorticoids within 4 weeks prior to the baseline or use of narcotic analgesics except for analgesics permitted within the framework of the study (codeine and tramadol)
3. Presence of another, serious chronic-inflammatory disease
4. Positive hepatitis B antigen (HBsAg), hepatitis C antibodies and/or HIV antibodies.
5. Presence of a relevant, active infection or other diseasees, which entail a tendency towards infection, including HIV-positive upon screening (ELISA and Western blot)
6. Positive screening for latent tuberculosis, in accordance with usual local practice. If patient is taking adequate/isoniazid prophylaxis for 4 weeks before first IP administration, this patient may be randomized.
7. Raised liver count (raised bilirubin; ALT or AST ≥ 3-fold of normal range)
8. Serum-creatinine concentration > 1.5 mg/dl
9. Inadequate haematological findings (Hb ≤ 9 g/dl, neutrophils ≤ 2,500/µl and thrombocytes ≤ 100,000/µl)
10. Simultaneous participation in any other interventional clinical study within the last 30 days preceding the commencement of the study
11. History of neoplasia with the exception of a curatively treated non-melanoma skin tumour or carcinoma of the cervix treated in situ without any indication of recurrence within the last 10 years
12. Relevant cardiac or pulmonary disorders
13. Severe intercurrent neurological or psychiatric disorders

14. Macrophage activation syndrome (MAS) within the framework of a previous treatment with IL-1 blockade (e.g. anakinra, rilonacept)
15. Vaccination with a live vaccine within 3 months before baseline
16. Alcohol or drug abuse in the past 12 months
17. ≥ 400 ml donation of blood or –loss up to 8 weeks before baseline
18. Pregnancy or breast-feeding
19. Commitment of the patient to an institution at the direction of an authority or court

3.2.3. Selection of patients for LTE

1. Participation in the randomized, placebo-controlled trial (CACZ885GDE01T) (core-study)
2. Considered to be a responder with respect to articular involvement (according to EULAR response criteria) as well as to systemic disease manifestation of AOSD
3. If the patient is of childbearing potential, she agrees to: comply with effective contraceptive measures, has been using adequate contraception since the last menses, will use adequate contraception during the study, and has a negative pregnancy test within one week of study entry

3.3. Study treatment

3.3.1. Clinical study drug and dosing

Canakinumab 150 mg/ 1ml solution for injection will be used as the study substance in a dose of 4mg/kg body weight up to a maximum of 300 mg subcutaneously. Individual administration dose will be calculated based on the subject's body weight as measured at the baseline and subsequent scheduled visits. A fixed dose level of 4mg/kg (to a maximum of 300 mg) will be used for the calculation.

- Example of calculation (patient requiring 4mg/kg):
  - Subject weight = 60 kg
  - Dose level = 4mg/kg
  - Calculated dose (mg) = 60 kg x 4mg/kg = 240 mg
  - Calculated volume of solution for s.c. injection (mL): 240 mg/150 mg/mL = 1.6 mL
  - Number of vials to be used: 2

The placebo will be administered as an identical injection.

3.3.2. Clinical study material in the long-term extension

In the LTE, open-label canakinumab will be used for treatment.

3.3.3. Preparation, handling and storage of the study drug

Canakinumab / placebo for subcutaneous injection

Novartis will provide canakinumab as solution to prepare a subcutaneous injection.

The canakinumab 150mg/ 1mL solution for injection is provided in 2mL glass vial filled with 1.0 mL of solution, plus 15% overfill (0.15 mL) to allow a complete withdrawal of 1.0mL of solution from each vial. Packs and vials will be provided as both blinded and open label presentations.
Canakinumab 150mg/ 1mL solution for injection is a clear to opalescent, colorless to yellowish, ready to use solution formulated in L-histidine buffered mannitol solution containing polysorbate 80.
As canakinumab is a protein, the solution can contain some translucent particles.

Each vial is intended to be used for a single application. All residues of canakinumab remain in the vials. Any remaining quantities of the study substance must not be used for application in other study participants/ patients.
The sponsor will provide study sites with supplemental material.

Placebo

Novartis will provide placebo solution for injections in 2mL glass vial filled with 1.0 mL of solution plus a 15% overfill (0.15 mL) to allow a complete withdrawal of 1.0mL of solution from each vial. Packs and vials will be provided as blinded presentations.
Placebo solution for injection is a clear to opalescent, colorless to yellowish, ready to use solution formulated in L-histidine buffered mannitol solution containing polysorbate 80.

Each vial is intended to be used for a single application. All residues remain in the vials. Any remaining quantities must not be used for application with other study participants/ patients.

Instructions regarding the preparation of canakinumab / placebo solution for subcutaneous injections

An independent qualified member of staff is not necessary; each trained staff member can prepare and administer the study drug.

The vials with solution have an overfill of 15% above the nominal quantity. No more than 1.0 ml may be drawn.
Materials required:

- Canakinumab 150mg /1mL or placebo solution for injection
- Sterile 1 mL (10µL graduated) disposable syringes for withdrawal and injection of the solution for s.c. injection.
- Sterile disposable needles 21G x 2" for withdrawal of investigational treatment solution from the vial; if not available, needles with larger inner diameter can also be used.
- Sterile disposable needles 27G x 0.5" for s.c. injections.

Remove the plastic flip off cap from the vials and disinfect the rubber stopper with an alcohol swab. Using a clean 1.0mL syringe to withdraw the calculated volume of solution from each vial.

Administration

Canakinumab injection solution or placebo is to be injected subcutaneously with a 27Gx0.5"needle. The dose adapted according to body weight is to be injected subcutaneously on each dosage day. Dosage should be made in the morning so as to have time for taking blood samples and well as processing and despatching the blood samples. The patients must be observed for 30 minutes after the administration of the study drug at the test centre.
In the LTE (i.e. after week 24), the medication will be administered open-label. In the LTE placebo will not be applied.

Storage of the study drug

The study drug is to be stored at temperatures between 2 and 8° C in the refrigerator of the respective participating centres. If not used immediately (within 15 minutes) after preparation the solution should be kept at 2-8 °C, and allowed to come to room temperature for approximately 20 minutes before administration. ACZ885 solution for injection can be stored at 2-8 °C for up to 24 hours. Do not freeze. It will be administered to the patients in the masked part of the study at baseline as well as at weeks 4, 8, 12, 16 and 20 at the study centre.

After and including week 24, administration of study drug will be performed in an open-label setting.

3.3.4. Down-titration, dose modification and discontinuation of treatment

The patients will be treated with canakinumab at a dose of 4mg/kg body weight up to a maximum of 300 mg or the placebo at 4-week intervals with no dose modification being foreseen until week 20. One application at most can be missed during the core study period.

Long term extension

There will be the possibility of a down-titration from 4mg/kg/BW (max. 300mg)/month to 2mg/kg/BW (max 150mg)/month that might be performed after week 28 (visit 9) if the patient fulfils remission criteria defined as: a DAS28 < 2.6 AND no signs of systemic activity (Yamaguchi´s primary classification criteria for AOSD) for two consecutive visits.
In case of increasing disease activity or flare under a reduced dosage of canakinumab, up-titration to the initial dosage is possible.

3.3.5. Allocation of the study medication / randomisation

34 patients will receive treatment with the study substance (canakinumab) and 34 patients will receive treatment with a placebo. The patient's report will be made by FAX randomisation form. Randomisation will be made on the basis of a documented randomisation list.
A re-evaluation will take place in week 12. It is expected that at this point in time, approx. 75% of patients will change over from the placebo to the verum group, if no significant improvement has been achieved according to the DAS28 (a significant improvement is defined as improvement in the DAS28 from the commencement of the study (=average of visits 1 and 2) to visit 5 of more than 1.2 points).

During the LTE all patients will receive canakinumab open-label.

3.3.5 Blinding, packaging and labelling

Blinding, packaging and labelling will be performed by Novartis Pharma.
There will be 1,008 complete, packed and marked samples of canakinumab (Ilaris®) 150 mg and 768 complete, packed and marked samples with placebo for the placebo-controlled core-study.

There will be approx. 1440 - 1680 fully packed and labelled samples of canakinumab (Ilaris®) 150 mg for the LTE.

3.3.6 Concomitant medication

Concomitant systemic treatment with glucocorticoids is excluded in a dose of 10 mg/day of prednisolone-equivalent or biologicals (infliximab, adalimumab, etanercept, abatacept, rituximab, tocilizumab, anakinra). In cases of existing DMARD treatment, this must have been stable for 3 months. The use of narcotic analgesics, with the exception of analgesics permitted within the framework of the study (codeine and tramadol), is not permitted. NSAIDs and oral glucocorticoids (≤ 10 mg/day Prednisolone-equivalent) must be taken at a stable dose at least 1 week before baseline and should not be changed within the period of participation in the study, as far as possible.
Concomitant medication taken for the treatment of other illnesses will be recorded at every visit in regards to dose, type of application and indication.

3.4. Study procedures by visit

Visit 1-Screening (week -4 to -1)

- Informed consent, including accompanying project, if applicable
- Demographic data
- Medical history
- Physical examination and vital signs
- Concomitant medication
- Inclusion and exclusion criteria
- Differential blood count, Na, K, crea, ALT, AST, GGT, AP, LDH, ferritin, CRP
- ESR
- Protein electrophoresis
- Pregnancy test
- ANA
- HIV, hepatitis B and heptitis C serology (HBsAg, Anti-HCV)
- Urine test sticks
- Tb screening (chest X-ray ≤ 3months, PPD skin test and/or IGRA)
- Joint status (68)
- PGA
- PhGA
- Pharmacodynamics

Visit 2-Baseline (day 0)

- Informed consent for accompanying project§
- Physical examination and vital signs
- Concomitant medication
- Inclusion and exclusion criteria
- Adverse events
- Differential blood count, Na, K, crea, ALT, AST, GGT, AP, LDH, ferritin, CRP
- ESR
- Anti-canakinumab antibodies
- Urine test sticks
- ECG
- Joint status (68)
- Joint mobility
- PGA
- PhGA
- HAQ-DI, SF-36
- Pharmacodynamics
- Pharmacokinetic properties
- Administration of the study drug
- Biomarkers (with supplementary informed consent for the accompanying project)
- Randomisation FAX

Visit BM (day 7-10)

- Adverse events
- Biomarkers (with supplementary informed consent for the accompanying project)

Visit 3 and 4 (week 4 and 8 [+/-3 days])

- Physical examination and vital signs
- Concomitant medication
- Adverse events
- Diff. blood count, Na, K, crea, ALT, AST, GGT, AP, LDH, ferritin, CRP
- ESR
- Anti-canakinumab antibodies
- Joint status (68)
- PGA
- PhGA
- Pharmacodynamics
- Pharmacokinetic properties
- Administration of the study drug
- Biomarkers (visit 3 with supplementary informed consent for the accompanying project)

Visit 6 and 7 (week 16, 20 [+/-3 days])

- Physical examination and vital signs
- Concomitant medication

- Adverse events
- Diff. blood count, Na, K, crea, ALT, AST, GGT, AP, LDH, ferritin, CRP
- ESR
- Anti-canakinumab antibodies
- Joint status (68)
- PGA
- PhGA
- Pharmacodynamics
- Pharmacokinetic properties
- Administration of the study drug, if applicable

Visit 5 (week 12), [+/-3 days]

- Physical examination and vital signs
- Concomitant medication
- Adverse events
- Diff. blood count, Na, Ka, crea, ALT, AST, GGT, AP, LDH, ferritin, CRP
- ESR
- ANA
- Anti-canakinumab antibodies
- Joint status (66/68)
- Joint mobility
- PGA
- PhGAHAQ-DI, SF-36
- Pharmacodynamics
- Pharmacokinetic properties
- Re-evaluation of treatment (ΔDAS28 > 1.2)
- Fax to sponsor for re-randomisation in case of DAS difference ≤ 1.2
- Administration of the study drug, if applicable

Visit 8 (week 24), [+/-3 days]

- Physical examination and vital signs
- Concomitant medication
- Adverse events
- Diff. blood count, Na, K, crea, ALT, AST, GGT, AP, LDH, ferritin, CRP, ESR
- Electrophoresis
- Pregnancy test
- ANA
- Urin test stick
- ECG
- Anti-canakinumab antibodies
- Joint status (68)
- Joint mobility
- PGA
- PhGA
- HAQ-DI
- SF-36
- Pharmacodynamics
- Pharmacokinetic properties

- Pharmacodynamics
- Pharmacokinetic properties
- Biomarkers (with supplementary informed consent for the accompanying project)
- For patients eligible for LTE, administer open-label canakinumab

End of core study 1, 2 (week 28/40) [+/-3 days] for patients not classifying to participate in the LTE

- Physical examination and vital signs
- Concomitant medication
- Adverse events
- Diff. blood count, Na, K, crea, ALT, AST, GGT, AP, LDH, ferritin, CRP, ESR
- ANA
- Anti-canakinumab antibodies

Long term extension

Visit 9 - 31 (week 28/month 7 – month 30), [+/-7 days] (for patients classifying to participate in the LTE) monthly visits

- Physical examination and
- vital signs
- Concomitant medication
- Adverse events
- Diff. blood count, Na, K, crea, ALT, AST, GGT, AP, LDH, ferritin, CRP, ESR
- Anti-canakinumab antibodies
- PGA
- PhGA
- Pharmacodynamics
- Pharmacokinetic properties
- Administration of the study drug, if applicable
- Joint count (28)
- Joint count (66/68)
- Joint mobility
- HAQ-DI
- SF-36

} to be performed every 3 months and at month 30 (months 9, 12, 15, 18, 21, 24, 27)

Visit 32/Month 33/EOS-LTE

- Physical examination and vital signs
- Concomitant medication
- Adverse events
- ECG
- Diff. blood count, Na, K, crea, ALT, AST, GGT, AP, LDH
- Ferritin
- CRP
- ESR
- Electrophoresis
- ANA
- Anti-canakinumab antibodies
- Urin test stick

3.5. Duration of treatment and participation of the patients

Participation in the core study and LTE, including screening and subsequent observation, will involve a maximum of 34 months (4 weeks screening, 30 months study-drug treatment, 3 months FU). The study substance will be taken through a maximum of 30 applications over a period of a maximum of 30 months.

3.6. Termination of the treatment or of participation in the study

Criteria for discontinuing the treatment or participation in the study in individual cases:

1. Withdrawal of consent to participate
2. Adverse events which make it appear that continuation of the treatment/participation can no longer be seen as medically justifiable
   a. Parameters which can be measured medically (derived from the safety profile/side-effects of the study medicine)
      I. Appearance of recurrent and/or severe infectious diseases
      II. Occurrence of serious adverse events which are not compatible with the further administration of the study drug
      III. Occurrence of a malignant neoplasm
      IV. Occurrence of macrophage activation syndrome (MAS)
      V. Occurrence of pregnancy
      VI. Rise in liver function values (incl. bilirubin; ALT or AST > 5-fold normal range)
      VII. Rise in creatinine > 30%
      VIII. Neutropenia < 1,000/µl
      IX. Leukocytopenia < 2000/µl
      X. Thrombocytes < 50,000/µl
   b. High activity of the AOSD persisting or newly occurring since the inception of the study

In the event of premature discontinuation or termination of the study through a decision by the sponsor, the investigating doctor or the study participant, the visit will be carried out at week 28. Furthermore, a concluding visit will be held, recording the adverse outcomes with an interval of 20 weeks after the last administration of the study drug.
The participants in the study will be transferred for further rheumatological treatment to the respective responsible/referring treatment institution after the study has been concluded.

3.7. Efficacy, pharmacodynamics and pharmacokinetics, analysis of safety

3.7.1. Study of efficacy

The following investigations will be conducted in order to study the efficacy of canakinumab: clinical and also serological tests will be conducted in order to assess joint involvement and the disease activity of AOSD. Efficacy with regard to joint involvement will be studied on the basis of the findings about the joints. The following are envisaged as valid methods for examining tolerance of the study drug:

Joint status:
Number of tender joints (68 joints)
Number of swollen joints (66 joints)
Global patient's assessment regarding disease activity and pain (numerical rating scale (NRS) 0-10)
Global physician's assessment regarding disease activity (NRS 0-10)
Illness activity with regard to joint involvement (DAS28 and ACR response criteria)
Joint mobility based on the neutral zero method

Assessment of functionality and life quality
Health Assessment Questionnaire - Disability Index (HAQ-DI)
SF-36 health survey

Laboratory tests
Serological markers for inflammatory reactions (ESR, CRP, ferritin)

Further optional investigations
The optional scientific accompanying project on biomarker analysis includes the following investigations:

1) Investigations into soluble serum proteins
at baseline, day 7-10 and week 4 and during an episode of illness, macrophage activation syndrome (MAS), or suspected MAS:
   - IL-6 (2 ml blood in the serum test tube for 600 µl serum)
   - IL-18 (2 ml blood in the EDTA test tube for 600 µl plasma)
   - IL-18, IL-18-BP and IL-18/IL18-BP complex (5 ml blood in the Heparin test tube for 2ml plasma and 5ml blood in the serum test tube for 2 ml serum)

at baseline, day 7-10 and week 4 and during an episode of illness
   - S100 protein (4 ml blood in the serum test tube for 2 ml serum)

2) Investigations into the mRNA-expression
at baseline, day 7-10 and week 4 and during an episode of illness, macrophage activation syndrome (MAS), or suspected MAS:
   - PAXgene (2.5 ml blood in the PAXgene test tube)
   - Mononuclear cells of the peripheral blood [PBMC] (8 ml blood in the Vacutainer®CPT™ cell preparation test tube with sodium citrate)

3) Pharmacogenetic investigations (10 ml whole blood)
at baseline:
   - Identification of genome sequencing and Single Nucleotide Polymorphisms [SNP].

3.7.2. Pharmacodynamics and pharmacokinetics

The serum-canakinumab concentration will be established at all visits and during episodes of illness (2 ml serum test tubes). In the event of an anaphylactic reaction, samples will be investigated following the injection and at intervals of 8 weeks.

Overall, IL-1ß (circulating IL-1ß as well as attached to canakinumab) will be investigated at all visits (3 ml serum small tubes).

3.7.3. Safety investigations

The following investigations will be carried out in order to ensure the safety of the application of canakinumab:

a. Blood count, electrolyte levels, (Na, K), blood chemistry (ALT, AST, GGT, AP, ferritin, LDH, creatinine and urine test sticks at each visit)
b. Recording of adverse events over the entire period
c. Recording of vital signs and physical examination at each visit
d. Immunogenity (anti-canakinumab antibodies and ANA) (1 ml serum test tubes)

Clinically significant outcomes of examinations of the laboratory diagnostic investigations will be evaluated as an adverse event and recorded in the case report form (CRF). Clinically not significant examination results from laboratory diagnostic investigations will be recorded in the source documents (patient records).

Treatment with canakinumab will be discontinued in the event of: the occurrence of a pronounced renal function disorder (increase exceeding 5-fold of the norm), increase in creatinine by > 30%, leukocyptopenia of < 2.0 x 10^9/l, neutropenia of < 1.0 x 10^9/l and thrombocytopenia < 50.0 x 10^9/l, occurrence of an allergic reaction, occurrence of macrophage activation syndrome, occurrence of pregnancy.
Therapy with canakinumab will be suspended in the event of liver counts increasing between 3- and 5-fold of the norm.

3.8. Remission criteria and down titration

There will be the possibility of a down-titration from 4mg/kg/BW (max. 300mg)/month to 2mg/kg/BW (max 150mg)/month after week 28 (visit 9) if the patient fulfils remission criteria.

Remission criteria are defined as:
DAS28 < 2.6
AND
no signs of systemic activity defined as any of Yamaguchi´s primary classification criteria for AOSD for two consecutive visits.

3.9. Definition of flare or increasing disease activity

An increasing disease activity or flare is defined as the onset of signs of systemic activity defined as any of Yamaguchi´s primary classification criteria for AOSD and the elevation of the CRP-value and/or ferritin-value ≥ 3x upper normal range.

4. Adverse events

4.1. Definition

4.1.1 Definition of adverse events

An adverse event (AE) is every adverse medical event which occurs in a patient or a participant in a clinical study following the administration of a drug and which is not necessarily in a causal relationship with this treatment.
An adverse event can therefore mean every unfavourable and unintended reaction (including an abnormal laboratory test finding), every symptom or every illness temporarily accompanying the administration of a drug (of a study drug in this case), whether this is connected to the study drug or not.

4.1.2. Definition of serious adverse events

A serious adverse event (SAE) is every adverse medical event which:

- Leads to death
- Is life-threatening
- Requires inpatient treatment of the study participant or which
- Makes an extension of the in-patient stay necessary
- Leads to permanent or significant damage/disabilities, or which
- Represents an innate malformation or a congenital abnormality

4.1.3. Definition of an unexpected, adverse drug interaction (SUSAR)

A SUSAR is a serious adverse event in which a causal connection exists between the administration of the study drug and the event and in which the type and severity of the event does not correspond with the information already known about the study drug.

4.2. Procedures for reporting adverse events and serious adverse events

The investigating physician will regularly monitor all patients with respect to the occurrence of adverse events in clinical and laboratory chemical terms.

If a serious adverse event occurs, then this is to be reported to the sponsor within 24 hours. The investigating physician will evaluate and record every adverse event in detail, with at least the patient number, (pseudo-) initials, causal connection with the study drug, degree of severity, start and end dates and medication, as well as other therapies for the treatment of the adverse event being recorded. In addition, the age, alternative aetiology, relevant previous and concomitant diseases, concomitant medication / treatments will be recorded, together with any laboratory results of relevance to this event.

If adverse, serious and at the same time unexpected drug interactions (SUSAR) occur, the sponsor (simultaneously principal investigator) will inform all participating investigating

physicians without delay. Furthermore, the responsible ethics committee, authority (PEI) and manufacturer of the study drug will be informed within the regular periods of time.

5. Determining the statistical evaluation of the study

Statistical evaluation will be conducted according to the intention-to-treat (ITT) principle. All patients who are included in the CONSIDER (CACZ885GDE01T) double blind, placebo-controlled clinical study will have been allocated to one of the two study arms on a randomised basis, and have received at least one dose of the study drug (modified ITT population) will be included in the statistical evaluation of the study into the safety and efficacy analysis of canakinumab in patients with AOSD and active joint symptomatology.

5.1. Testing of the efficacy of canakinumab

The primary objective consists in comparing the proportion of DAS28 responders at week 12 between the two treatment arms. A DAS28 responder is a patient whose DAS28 score has improved by more than 1.2 points between the commencement of the study and week 12. Patients who have terminated participation in CONSIDER (CACZ885GDE01T) before week 12 will be counted as non-responders. As the starting value which forms the base for calculating the improvement, the mean value of the DAS28 scores from visits V1 (screening visit) and V2 (week 0) will be used. Comparison of the response rates will then be made by using R.A. Fisher's exact test with a two-tailed level of significance of $\alpha = 0.05$. 95% confidence intervals for the proportion of responders will be calculated using the Blyth-Still-Casella method.

Comparison of the secondary endpoints will be performed in a similar way: ACR 20, ACR 50, ACR 70 (EULAR good response) DAS28 remission (DAS28 < 2.6), low disease activity (DAS28 < 3.2) at week 12. In this process, the ACR response criteria will be examined on the basis of the 68/66 joint scores, the HAQ-DI, the erythrocyte sedimentation rate, the patient's assessment of pain and disease activity and the physician's assessment of disease activity.
Mean values will be compared by means of a t-test or, if required due to the skewness of distribution (in part. laboratory data such as ESR, CRP, ferritin), the Mann-Whitney test.
The outcomes of treatment at week 24 will be compared with the values achieved at week 12 in the patients randomised into the verum group. The McNemar test for binary outcome parameters and the paired t-Test or Wilcoxon test will be used for this purpose. Evaluation will be performed in a similar way within the 2 sub-groups of the placebo group: of patients who have been switched due to insufficient responsiveness to canakinumab as well as of patients who have been treated for 24 weeks with the placebo. For the latter sub-group, the proportion of patients who were in DAS28 remission at week 24 as well as overall between week 12 and 24 will be of particular interest. This proportion will be given as a percentage of all placebo patients, with the associated 95% confidence intervals being calculated according to the Blyth-Still-Casella method.

5.2 Calculation of the sample size

The primary objective consists in proving - in comparison with patients treated with placebos - a significantly increased DAS28 response by patients with AOSD and joint involvement who have been treated for 12 weeks with canakinumab.
The HO zero hypothesis assumes that treatment with canakinumab will not have any significant influence upon joint involvement in AOSD. The H1 alternative hypothesis assumes that treatment with canakinumab will lead to a clinically significant improvement in joint involvement in patients with AOSD.
The studies and case reports of AOSD patients who have been treated with an IL-1 inhibitor (anakinra) which have been available to date lead to the expectation that a very high response rate will be produced in the verum group. Laskari et al. report that in 21/25 (84%) AOSD patients "the clinical activity resolved completely". We found a similar result in a study of our own on 8 AOSD patients treated with anakinra, who all achieved remission. There is, unfortunately, no valid data regarding the assessment of the DAS28 responses in response to placebos. Based on our experience in treating Still's Disease patients, a placebo response rate of a maximum of 25% can be assumed. With the cautious assumption of a verum response of at least 67%, 34 patients per group would accordingly be sufficient to achieve an at least 90% power of Fisher's exact test. This number of cases would also be sufficient if the placebo responses amount to 33% and we would assume a slightly increased verum response of at least 70% in this case. The total of 34 patients per group would then still correspond to an 80% power. i.e. lead to a significant result with at least 80% probability, a two-tailed Fisher test with an alpha of 5%. As a result, the number of patients is set at 34 per treatment arm.

Participants from the randomized, placebo-controlled trial can continue treatment with canakinumab in the LTE study. Taking into account an estimated drop-out rate of about 30% of the remaining 43 patients to be enrolled, approx. n=~~30 -~~ 35 patients from the RCT will continue treatment in the LTE.

5.3. Randomisation and stratification

Randomisation will take place centrally at the [redacted] ([redacted]), Berlin following previous treatment with biologicals (yes/no) by means of permuted block randomisation. After week 12, a re-allocation of the treatment arm will be required for a portion of the patients. This is described in more detail in "early escape".

5.4. "Early escape"

Patients who have been randomised into the placebo group and have improved in week 12 by less than 1.2 points based on DAS28 compared with the start of the study (DAS28 non-responders) will be treated with canakinumab after week 12. This requires that for every patient who has completed visit 5 (week 12), the corresponding CRF pages of visits V1, V2, V5 on which the details are stated which are required to calculate the DAS28 be sent to the randomisation office in the [redacted]. A calculation of the DAS28 response for the patients will then be made there and the re-allocation of the medication will be derived from this.

Patients in both the placebo and verum groups will remain in their respective treatment arms upon achieving a DAS28 response in week 12.
DAS28 non-responders of the placebo group in week 12 will openly receive canakinumab at weeks 12, 16 and 20.
DAS28 non-responders in the verum group in week 12 will not receive any further study medication and will be continued until the concluding visit in week 28.

5.5. Dealing with missing or incomplete data

Patients who have terminated the study prematurely will be regarded as non-responders with regard to all parameters of efficacy from the time they end the study (see above). Missing values for individual visits preceding a drop-out visit (if available) will be replaced by the SAS procedure, PROC MI by means of the Markov Chain Monte Carlo method and the criteria derived will then be re-calculated. Should the number of variables and group to be replaced in each case not exceed 15%, then repeated replacements will not be made. In order to then be able to make comparisons of mean values, the replacement of missing values from visits will be made according to drop-out. Replacement is likewise made by means of PROC MI with the use of regression techniques, with repeated substitution if necessary.

5.6. Statistical methods

5.6.1. Comparisons at baseline

A comparative examination at baseline is required.

5.6.2. Analysis of efficacy

Primary endpoint

- Fisher's exact test will be applied to compare the number of patients with a clinical relevant reduction of the DAS28 (> 1.2 units, primary endpoint) within the mITT population between the treatment groups at week 12. (See 5.1)

The secondary endpoints of the core study:

- Evaluation of the safety of canakinumab in patients with AOSD
- Evaluation of the efficacy of canakinumab in patients with AOSD and joint involvement according to the ACR response criteria at weeks 12 and 24
- Proportion of the patients achieving low disease activity (DAS28 < 3.2) or remission (DAS28 < 2.6)
- Examination of the changes in health status based on HAQ-DI and SF-36
- Improvement in skin manifestation of AOSD
- Reduction in inflammatory markers (CRP, ESR, ferritin),
- Biomarker analysis (mRNA, proteins) with the aim of enabling a prognostic statement to be made regarding responsiveness to the treatment.
- Regarding the statistical methods see 5.1.

The primary objective parameter of the long term extension study is:

- The evaluation of long-term safety of canakinumab in patients with AOSD and articular involvement. Safety analysis will consider the exposure time. Event rates per 100 patient years and their corresponding 95% confidence intervals will be calculated.

The secondary objective parameters of the long term extension study are:

- First results will be provided on the disease course of AOSD patients treated with canakinumab under a treatment strategy which allowed down-titration of the canakinumab dose as described above.
- The long-term efficacy of canakinumab in patients with AOSD will be described according to EULAR response criteria (proportion of patients showing prolonged clinically improvement according to DAS28 low-disease activity [< 3.2] and remission [< 1.2], reduction of flares and glucocorticoid intake)
- Assessment of health outcome measures (HAQ-DI), improvement in skin manifestation and reduction of inflammatory markers of disease under long-term treatment
- The impact of the change in the dosage of canakinumab on the disease course will be examined..

5.6.3. Evaluation of safety

Data relating to safety will be evaluated after the incidence and type of adverse events occurring have been s
ummarised. All patients will be included in the evaluation of the safety data.
Evaluation of long-term safety of canakinumab in patients with AOSD and articular involvement is the primary objective of LTE study.

5.7. Interim analysis

A primary endpoint analysis is planned when all patients finish week 24 of the core study.

A safety interim analysis is planned one year after LPFV in LTE.

6. Administrative provisions

6.1. Good Clinical Practice

This study will be conducted in accordance with the guidelines of the International Conference for Harmonisation (ICH), "Good Clinical Practice" (GCP) as well the federal and regional laws of the authorities. The principal investigator will be entrusted with the appropriate use of the study drug in the ways described in the protocol or in the technical information. The consistent collection of essential clinical documents will ensure the integrity and validity of the entire data. A primary study file (referred to as the master file) will be opened when the study commences, be updated during the study and stored according to the guidelines following the study.

6.2. Ethical provisions

This study will be conducted in accordance with the basic ethical principles of the Helsinki

Declaration (of 1996). An independent ethics committee will review the entire study documentation in order to ensure the protection of the patient, his rights and his well-being. The study protocol, patient information, patients' informed consent forms and data collection questionnaire will be submitted to an independent ethics committee, together with updates of any information on safety, advertisements (if applicable), interim reports and revisions of these documents.

6.3. Patient information and informed consent

Following extensive discussion, informed consent will be collected in written form from each patient or their legal representative. The procedure for collecting the informed consent and its documentation and contents will correspond to the GCP / ICH Guidelines and federal or regional legal provisions.

6.4. Patient confidentiality

In order to uphold the patient's right to confidentiality, all data to be recorded, such as lists of medication, study reports and all forms of communication within the study, will be encoded using an allocated patient number as well as pseudo-initials (e.g. A-A, B-B, etc.).

6.5. Compliance with the study protocol

The principal investigator will carry out this study in adherence with the protocol for which he has approval/positive opinion from an independent ethics committee and the corresponding regional authorities (PEI). Any amendments to the protocol require the written approval of an independent ethics committee or of the corresponding regional authority (PEI). Exceptions are only permitted in order to avoid a directly hazardous situation to the patient occurring. The independent ethics committee can, if the applicable authorisations allow this, bring about an accelerated approval of/ positive opinion on small changes to protocols in on-going studies, if an accelerated approval/ positive opinion has already been made available on the part of an independent ethics committee. The principal investigator will present all amendments to the protocol to the corresponding regional authorities in accordance with legal regulations. Any deviation from the study protocol must be recorded in full in the source data.

6.6. Audits and monitoring

The responsible regional and federal authorities and the ethics committee can demand access to all source data, data media and other study documents within the framework of an audit or an inspection. Direct access to these documents must be guaranteed by the principal investigator at all times.

In order to monitor this clinical study appropriately, an independent monitor will be commissioned to undertake a review of its due implementation and documentation. Six monitoring visits are scheduled to take place in the course of the core study.

Six visits for each active centre are scheduled to take place in the course LTE, i. e. initiation visit, ongoing monitoring every 6 months during study course and close out visit.

6.7. Accountability

Liability for the study drug lies within the area of responsibility of the principal investigator. He will ensure that the study drug will only be used in accordance with the study protocol. The whereabouts of the study medication will be recorded at the test centre. Accordingly, the receipt, administration to patients and destruction of the drug will be recorded in lists. Notes will be made of the date, number, batch number, shelf life and patient number. All materials containing canakinumab will be despatched separately to the respective test centres via the central pharmacy.

6.8. Early termination of the study

The study can be terminated early by the principal investigator for compelling reasons. However, the justification for this decision must be made in writing. Circumstances which can lead to premature discontinuation are, e.g. (not an exhaustive list):

- Unexpected, significant, unreasonable risk for the health of the patients
- Insufficient patients having been recruited
- Grave violations of the study protocol

6.9. Publication of the results of the study

The data collected for this study are to be treated confidentially. The participating investigating physicians agree that all of the information solely serves the purpose of the study and is not allowed to be used in any other way without the consent of the sponsor. It is envisaged that the results of this study will be presented at scientific events and will be published in peer-reviewed scientific or medical journals. The list of authors has been agreed with the authors prior to publication and confirmed by the principal investigator.

7. References

1. Bagnari V et al (2010) Adult-onset Still´s disease. *Rheumatol Int*.; 30(7): 855-62

2. Efthimiou P, Paik PK, Bielory L (2006) Diagnosis and management of adult-onset Still´s disease. *Ann Rheum Dis* 65: 564-572.

3. Pouchot J, Vinceneux P (2004) Manifestations cliniques et biologiques de la maladie de Still de ládulte. *Presse Med* 33:1012-1018.

4. Wouters JM, van de Putte LB (1986) Adult-onset Still´s disease; clinical end laboratory features, treatment and progress of 45 cases. *Q J Med* 61: 1055-1065

5. Pouchot J, Sampalis JS, Beaudet F et al (1991) Adult Still´s disease: manifestations, disease, course, and outcome in 62 patients*. Medicine* 70: 118-136.

6. Ohta A, Yamaguchi M, Tsunematsu T et al (1990) Adult Still´s disease: a multicenter survey of Japanese patients*. J Rheumatol* 17: 1058-1063.

7. Owlia MB, Mehrpoor G (2009). Adult-onset Still´s disease: a review. Indian J Med Sci. 2009 May;63(5):207-21.

8. Fautrel B (2008). Adult-onset Still disease. Best Pract Res Clin Rheumatol. 2008 Oct;22(5):773-92. Review.

9. Kontzias A, Efthimiou P (2008). Adult-Onset Still´s Disease-Pathogenesis, Clinical Manifestations and Therapeutic Advances. Drugs. 2008;68(3):319-37. Review.

10. Ohta A, Yamaguchi M, Kaneoka H, Nagayoshi T, Hilda M (1987) Adult Still´s disease: review of 228 cases from the literature. *J Rheumatol* 14: 1139-1146.

11. Kim HA, Sung JM, Suh CH (2011). Therapeutic responses and prognosis in adult-onset Still´s disease. Rheumatol Int 2011 Jan 29. [Epub ahead of print]

12. Zeng T, Zou YQ, Wu MF, Yang CD (2009). Clinical features and prognosis of adult-onset Still's disease: 61 cases from China. J Rheumatol. 36(5):1026-31.

13. Manger B. 2008. Der adulte Morbus Still. *Zeitschrift für Rheumatologie* 5.2008- S. 415-423.

14. Efthimiou P, Georgy S (2006). Pathogenesis and Management of Adult-Onset Still´s Disease. 2006 Dec; 36(3):144-52. Epub 2006 Sep 1.

15. Wendling D, Humbert PG, Billerey C, Fest T, Dupond JL (1990) Adult onset Still´s disease and related renal amyloidosis. Ann Rheum Dis. 1991 Apr;50(4):257-9.

16. Harrington TM, Moran JJ, Davis DE (1981) Amyloidosis in adult onset Still´s disease. J Rheumatol. 1981 Sep-Oct;8(5):833-6

17. Oh YB, Bae SC, Jung JH, Kim TH, Jun JB, Jung SS, Lee IH, Yoo DH, Park MH, Kim SY (2000). Secondary renal amyloidosis in adult onset Still's disease: case report and review of the

literature. Korean J Intern Med. 2000 Jul;15(2):131-4. Review.

18. Efthimiou P, Kontzias A, Ward CM, Ogden NS (2007). Adult-onset Still's disease: can recent advances in our understanding of its pathogenesis lead to targeted therapy? Nature Clinical Practice Rheumatology 2007 Jun; 3 (6): 328-335.

19. Magadur-Joly G, Billaud E, Barrier JH, et al (1995). Epidemiology of Adult Still´s disease: estimate of the incidence by a retrospective study in west France. Ann Rheum Dis 1995; 20:1608.

20. Evensen KJ, Nossent HC (2006), Epidemiology and outcome of adult-onset Still´s disease in Northern Norway. Scand J Rheumatol. 2006 Jan-Feb; 35 (1): 48-51.

21. Masson C, Le Loët X, Liote F et al (1995) Adult Still´s Disease: part I. Manifestations and complications in sixty-five cases in France. *Rev Rheum Engl* Ed 62: 748-757.

22. Masson C, Le Loët X, Liote F et al (1995) Adult Still´s Disease: part II. Management, outcome, and prognostic factors. *Rev Rheum Engl* Ed 62: 758-65.

23. Laskari K, Tzioufas AG, Moutsopoulos HM (2011) Efficacy and long-term follow-up of IL-1R inhibitor anakinra in adults with Still´s disease a case-series study *Arthritis Research & Therapy* 13:R91

24. Kötter I, Wacker A, Koch S et al (2007) Anakinra in Patients with treatment-resistant adult-onset Still´s disease: four case reports with serial cytokine measurements and a review of the literature. *Semin Arthritis Rheum* 37:189-197.

25. Naumann L, Feist E, Burmester GR et al (2010) IL-1-receptor antagonist anakinra provides long-lasting efficacy in the treatment of refractory adult-onset Still´s disease. *Ann Rheum Dis* 69: 466-467.

26. Vasques Godinho FM, Parreira Santos MJ, Canas da Silva J (2005) Refractory adult Still´s disease successfully treated with anakinra. *Ann Rheum Dis* 64: 647-648.

27. Fitzgerald AA, LeClercq SA, Yan A et al (2005) Rapid responses to anakinra in patients with refractory adult onset Still´s disease. *Arthr Rheum* 52: 1794-1803.

28. Nirmala N, Brachat A, Feist E, et al. Gene-expression analysis of adult-onset Still's disease and systemic juvenile idiopathic arthritis is consistent with a continuum of a single disease entity. Pediatr Rheumatol Online J 2015;13(1):50.

29. Rachel L, Glaser MD, Goldbach-Mansky R (2008) The spectrum of monogenic Autoinflammatory syndromes: understanding disease mechanisms and use of targetes therapies *Curr Allergy Asthma Rep* 8: 288-298.

30. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, Gitton X, Widmer A, Patel N, Hawkins PN (2009) Use of Canakinumab in the Cryopyrin-Associated Periodic Syndrome. N Engl J Med. 360(23):2416-25.

31. Feist E, Burmester GR (2010) Canakinumab for treatment of cryopyrin-associated periodic syndrome *Exp Opin Biol Ther* 10: 1631-1636.

32. Fachinformation Ilaris® Novartis Pharma (Mai 2010)

33. Ruperto N, Quartier P, Wulffraat N, Woo P, Loy A, Mouy R, et al. A phase II trial with canakinumab, a new IL-1beta blocking monoclonal antibody (ACZ885), to evaluate preliminary dosing, safety and efficacy profile in children with systemic Juvenile Idiopathic arthritis (sJIA) 15thPaediatric Rheumatology European Society (PreS) Congress London UK. 14–17 September 2008, Pediatric Rheumatology. 2008; 6:2.

34. Ruperto N, Quartier P, Wulffraat N, Woo P, Ravelli A, Mouy R, Bader-Meunier B, Vastert SJ, Noseda E, D'Ambrosio D, Lecot J, Chakraborty A, Martini A, Chioato A; Paediatric Rheumatology International Clinical Trials Organisation. A phase II, multicenter, open-label study evaluating dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features. Arthritis Rheum. 2012;64(2):557-67.

35. Yamaguchi, M., et al., Preliminary criteria for classification of adult Still's disease.*J Rheumatol*, 1992. 19(3): p. 424-30. http://dgrh.de/fileadmin/media/PraxisKlinik/Kriterien/PDFs/Stillsyndrom/Still.pdf

36. http://dgrh.de/fileadmin/media/Praxis___Klinik/Kriterien/PDFs/01-ra-10.pdf

37. Ravelli A, Magni-Manzoni S, Pistorio A, Besana C, Foti T, Ruperto N, Viola S, Martini A. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. *J Pediatr. 2005 May*; 146(5): 598-604. Review. PMID: 15870661 [PubMed - indexed for MEDLINE]

38. http://www.gesetze-im-internet.de/gcp-v/BJNR208100004.html

39. http://www.aerzteblatt.de/v4/plus/down.asp?typ=PDF&id=5324

8. Protocol signature

I hereby confirm the correctness of this protocol, together with all attachments which are enclosed with it. I undertake to conduct this study in adherence with the protocol, according to the currently valid guidelines and the statutory provisions currently in force.

Principal investigator	_____	_____	___ : ___ : _____
	Name	Signature	Date

9. Appendices

a. Index of abbreviations
b. Classification criteria for adult-onset Still's disease
c. DAS28
d. ACR score
e. Joint mobility neutral zero method
f. Macrophage Activation Syndrome (MAS) and MAS adjudication committee
g. GCP ordinance (version dated 9.8.2004)
h. Helsinki declaration (English version , including latest revision of October 2008)

Index of abbreviations

ACR	American College of Rheumatology
ADR	Adverse drug reaction
AE	Adverse event
ALT (GPT)	Alanine aminotransferase
AMG	German medicinal product act (Ger.: Arzneimittelgesetz)
ANA	Anti-nuclear antibodies
AOSD	Adult-onset Still´s disease
AP	Alkaline phosphatase
AST (GOT)	Aspartate aminotransferase
BfArM	Federal institute for drugs and medical devices (Ger.: Bundesinstitut für Arzneimittel und Medizinprodukte)
BM	Biomarker
CAPS	Cryopyrin-associated periodic syndromes
CINCA	Chronic infantile neurological, cutaneous, articular syndrome
Crea	Creatinine
CRF	Case report form
CRP	C-reactive protein
DAS28	Disease Activity Score 28
DMARDs	Disease modifying anti-rheumatic drugs
ESR	ESR - erythrocyte sedimentation rate [Ger.: Blutsenkungsgeschwindigkeit (BSG)]
EOC	End of core study
EOS	End of study
FCAS	Familial cold auto-inflammatory syndrome
FCU	Familial cold urticaria
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HAQ-DI	Health Assessment Questionnaire-Disability Index
Hb	Haemoglobin
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G
ITT	Intention to treat
K	Potassium
BW	Body weight
LTE	Long-term extension
LPLV	Last patient last visit
MAS	Macrophage activation syndrome
mg	Milligram
mmHg	Millimetre of mercury
MWS	Muckle Wells syndrome
Na	Sodium
NOMID	Neonatal onset multisystem inflammatory disease
NRS	Numerical rate scale
NSAR	Non-steroid anti-inflammatory drugs (NSAIDs)
PD	Pharmacodynamics
PGA	Patient global assessment
PhGA	Physician global assessment
PK	Pharmacokinetic properties
s.g.	salutis gratia

SAE	Serious adverse event
SF36	Short Form 36 - Questionnaire on state of health
SNP	Single nucleotide polymorphism
SUSAR	Suspected unexpected serious adverse reaction
VAS	Visual analogue scale

Classification criteria for Adult-onset Still's Disease (AOSD) according to Yamaguchi (1992)

Primary criteria
Fever attacks 39 °C, duration >1 week
Arthralgia
Salmon red, maculate, urticarial or maculo-papular rash
Leukocytosis of > 10 000/mm^3 with > 80% neutrophils

Secondary criteria
Sterile pharyngitis
Lymphadenopathy and/or splenomegaly
Hepatic enzymes increased
Negative rheumatoid factors and negative ANA

Exclusion criteria
I. Infection (esp. sepsis or mononucleosis syndrome)
II. Neoplasia (esp. lymphoma)
III. Rheumatic diseases or collagen disorders

According to the criteria published by Yamaguchi in 1992, 5 or more criteria must be met for classification, with at least 2 primary criteria needing to be fulfilled (sensitivity 96.2%, specificity 92.1%). Diagnoses I-III must be excluded. The criteria encompass clinical and laboratory chemical special features (17, 18, 34).

DAS28

The following parameters are included in DAS28:

- Number of joints tender to pressure (0-28; measurement of 28 in each case from the EULAR defined joints)
- Number of swollen joints (0-28)
- Erythrocyte sedimentation rate (mm/h)
- Assessments of disease activity by the patient (0-10 mm NRS)

DAS28 is calculated according to the following formula:

$$DAS28 = 0.56 \cdot \sqrt{\text{tender to pressure joints}+0.28} \quad \sqrt{\text{swollen joints}+0.70 \text{ in (ESR)}}+0.014 \text{ illness state}$$

- A value between 0 and 2.6: disease remission
- A value between 2.6 and 3.2: low disease activity
- A value between 3.2 and 5.1: moderate disease activity
- Values > 5.1: high disease activity

Standardised data entry forms and calculation aids are available for DAS28. (**http://www.das-score.nl/**)

ACR 20 50 70 Efficacy parameters

from http://dgrh.de/fileadmin/media/Praxis___Klinik/Kriterien/PDFs/01-ra-10.pdf (37)

≥ 20 (50/70)% improvement in the number of joints tender to pressure (68 joints)

and

≥ 20 (50/70)% improvement in the number of swollen joints (66 joints)

plus

≥ 20 (50/70)% improvement in 3 of the 5 following criteria:

- Statement of pain by the patient (NRS 0- 10)
- Assessment of disease activity of the patient (NRS 0- 10)
- Assessment of disease activity by the physician (NRS 0- 10)
- Patient questionnaire HAQ
- Acute phase reaction (ESR)

Joint mobility according to the neutral zero method

	Right	Left	Reference range (degree)
Shoulder joints			
External / internal rotation (upper arm contiguous)	/ /	/ /	40-60 / 0 / 40-60
Ante- / retroversion	/ /	/ /	150-170 / 0 / 40
Abduction / adduction	/ /	/ /	160-180 / 0 / 20-40
Elbows			
Extension / flexion	/ /	/ /	10 / 0 / 150
Pronation / supination	/ /	/ /	60-90 / 0 / 80-90
Wrists			
Extension / flexion	/ /	/ /	35-60 / 0 / 50-60
Radial / ulnar abduction	/ /	/ /	25-30 / 0 / 30-40
Hip joints			
Extension / flexion	/ /	/ /	0-10 / 0 / 120-140
Abduction / adduction	/ /	/ /	30-45 / 0 / 20-30
External / internal rotation (90° bent hip)	/ /	/ /	40-50 / 0 / 30-40
Knee joints			
Extension / flexion	/ /	/ /	5-10 / 0 / 120-150
Upper ankle			
Dorsal extension / plantar flexion	/ /	/ /	20-30 / 0 / 40-50
Pronation / supination	/ /	/ /	30-45 / 0 / 45-60

Macrophage Activation Syndrome (MAS)

Occurrence of biologic features of MAS such as haemorrhages, central nervous system dysfunction, hepatomegaly, serum fibrinogen level < 2.5 g/L, cytopenia, hypertriglyceridaemia, decreased platelet count, increased aspartate transaminase, hyperferritinaemia (Ravelli, Magni-Manzoni and Pistorio 2005) must be carefully monitored by the investigator. Significant findings which meet the definition must be recorded in the Adverse Event eCRF. See following section for the description of the MAS Adjudication Committee.

MAS Adjudication Committee

An independent Adjudication Committee will review and adjudicate information on all cases of MAS. Occurrence of MAS may be reported by investigators or through systematic database search of specified terms. The Committee will review cases as they are identified. The committee will be blinded to treatment if the patient has entered the blinded part of the study. A report of the adjudication outcome will be provided to the DMC and the Sponsor. As part of the adjudication process, a request for supplemental data collection will be sent to the investigator. The supplemental package will include standardized follow-up questions. If biological specimens (e.g. bone marrow aspirate, bronchoalveolar lavage, etc.) were collected as part of customary diagnostic work-up, samples, such as tissue slides, may be requested by the committee for their review and/or for specialized analysis such as immunohistochemical staining for biomarkers associated with MAS. As part of follow-up additional blood specimens for biomarker analyses may also be collected. Patients will provide written informed consent for providing additional specimens.

The MAS Adjudication Committee Charter provides detail on the committee composition, adjudication process, database search terms and supplemental data package. The outcome of the adjudication will be reported on the MAS adjudication CRF (37).

GCP Version dated 12.08.2004

from http://www.gesetze-im-internet.de/gcp-v/BJNR208100004.html(38)

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

from HYPERLINK "http://www.aerzteblatt.de/v4/plus/down.asp?typ=PDF&id=5324"
http://www.aerzteblatt.de/v4/plus/down.asp?typ=PDF&id=5324