Supplementary Data

Statistical Analysis – in detail

All of the patients who did not violate one of the following important inclusion criteria: diagnosis of adult onset Still's disease and disease activity based on DAS28 of ≥ 3.2 at screening were included in the efficacy analysis (in the ITT population – manuscript Figure 2).

Since in the placebo group two patients received one canakinumab dose each at week 4, an additional per-protocol (PP) analysis was carried out, from which these two patients were excluded. This was done after unmasking the statistical analysis team. For this reason, the PP analysis is not a new designed approach taking different aspects into account, but differs only in the above mentioned aspect from the major ITT analysis.

In order to be able to compare the course of the secondary efficacy parameter in both groups over the period of 12 weeks, a mixed linear model was used to compare treatment effects between the canakinumab and the placebo group by taking repeated measures of the outcome parameter into account.

Description of patients withdrawn during the first 12 week period

Up to week 12, four patients were withdrawn due to physician decision. One biologic-naïve female patient randomized to the canakinumab group was hospitalized due to the SAE hepatotoxicity and study medication was stopped. The patient recovered afterwards at week 8. Furthermore, three placebo patients previously treated with the IL-1 receptor antagonist anakinra were withdrawn within the first 10 days after baseline due to physician decision.

Long term extension (LTE) phase

All patients randomized to the core study who responded to treatment with the study drug (canakinumab or placebo) with respect to articular involvement [Δ DAS28(ESR)> 1.2] as well as to systemic disease manifestation of AOSD at week 24 (and who had their week 24-visit after March 2016) were able to enter the long-term extension phase (protocol version 3.0 date: 14/MAR/2016). In this phase patients (six female and one male aged between 24 and 70 years) were treated with open label canakinumab to capture long-term safety events and efficacy. Due to premature termination of the study, observation time was limited to a maximum of 27 months (reached only by one patient). In fact, four patients remained in DAS28 (ESR) remission (<2.6), whereas the remaining three patients were in low-disease activity (<3.2) for the full LTE period (one patient) or at least at last visit (two patients).

Table S1: Demographic and Disease characteristics by treatment group at baseline

		Canakinumab	**Placebo**
Parameter		**n=18**	**n=17**
Age	Range	(22; 62)	(24; 70)
Time since diagnosis (years)	Range	(0.1; 22)	(0; 14.3)
68 tender joint count	Median (IQR)	7.5 (5; 11)	6 (5; 11)
66 swollen joint count	Median (IQR)	5 (5; 6)	6 (4; 8)
Physician's global (NRS)	Mean (SD)	5.5 (1.5)	6 (2.1)
Patient's global (NRS)	Mean (SD)	6.89 (2.5)	6.53 (2.5)
Pain in the joints (NRS)	Mean (SD)	6.61 (2.6)	6.35 (2.7)
HAQ-DI	Mean (SD)	1.31 (0.6)	1.29 (0.8)
number of LOM joints	Mean (SD)	4.94 (3.7)	6.29 (3.8)
SF-36 physical health	Mean (SD)	29.39 (9.1)	28.73 (8.2)
SF-36 mental health	Mean (SD)	37.8 (9.1)	46.31 (13.7)

Physician's global: Physician's global assessment of disease activity, Patient's global: Patient's global assessment of disease activity (last 24 hours), Pain in the joints: Patient's assessment of pain in the joints (last 24 hours), number of LOM joints: number of joints with limitation of motion

Limitation of motion (LOM): The binary variable to indicate LOM for a joint was derived based on the evaluation of possible motion in different directions for that joint and the ability to reach the resting position. If more than half of values for a joint were missing, then LOM was set to missing. If at least one but less than half of values for a joint were missing, the joint was considered as joint with LOM. The number of joints with LOM was calculated as 12*(number of joints with LOM)/(number of available joint classifications).

Table S2: ITT-Comparison of DAS28 related disease activity parameters at week 12 by means of ANCOVA

		Canakinumab outcome at week 12		Placebo outcome at week 12		Group compar.	
Parameter	**mean at scr. bl**	**LSmean**	**95% CI LSmean**	**LSmean**	**95% CI LSmean**	**p-value param.**	**p-value nonpar.**
DAS28(ESR)	5.3	3.1	[2.4 ; 3.8]	4.32	[3.6 ; 5]	0.02	.
DAS28(CRP)	5	3.31	[2.7 ; 3.9]	4.16	[3.6 ; 4.8]	0.05	.
Patient's global	6	3.48	[2.3 ; 4.6]	4.85	[3.7 ; 6]	0.10	.
ESR (mm/h)	41.5	16.46	[7.8 ; 25.1]	27.98	[19.1 ; 36.9]	(0.07)	0.09
CRP (mg/L)	51.2	19.05	[6.3 ; 31.8]	28.76	[15.6 ; 41.9]	(0.29)	0.07
28 SJC	5.6	2.87	[1.5 ; 4.2]	3.85	[2.5 ; 5.2]	(0.32)	0.09
28 TJC	7	3.6	[2.2 ; 5]	4.6	[3.1 ; 6.1]	(0.34)	0.05

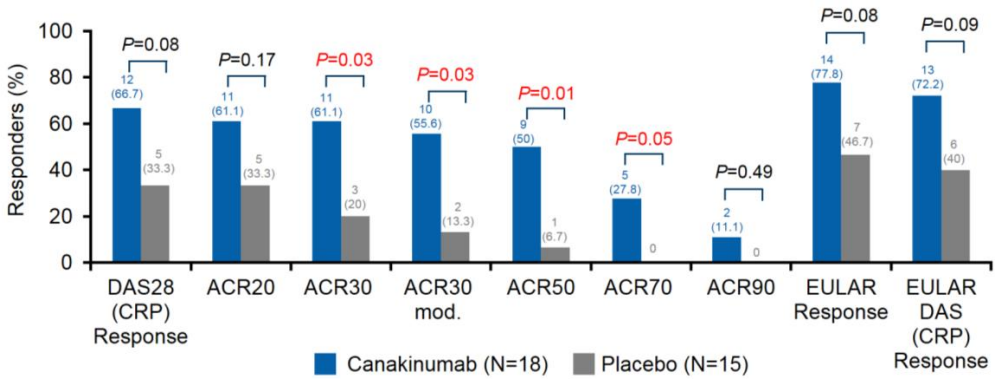
mean at scr. bl.: overall mean at screening and baseline of both groups used for adjustment, as obs.: as observed, 28 SJC: 28 swollen joint count, 28 TJC: 28 tender joint count, p-value param.: p-value of the parametric ANCOVA, p-nonpar: p-value of the nonparametric ANCOVA p-values in parentheses are given for comparison but are not used for interpretation. For the analysis of covariance (ANCOVA) of continuous variables at week 12, adjusting for baseline status, the LOCF method was applied to missing week 12 values.

Table S3: PP-Achievement of secondary response criteria at week 12

	Canakinumab		Placebo		
Outcome parameter	**responder n (%)**	**95% CI**	**responder n (%)**	**95% CI**	**p value**
DAS28 (CRP) Response	12 (66.7)	[43.1 ; 85.2]	5 (33.3)	[13.4 ; 59.2]	0.08
ACR20 week 12	11 (61.1)	[37.7 ; 81.1]	5 (33.3)	[13.4 ; 59.2]	0.17
ACR30 week 12	11 (61.1)	[37.7 ; 81.1]	3 (20)	[5.4 ; 45.3]	0.03
ACR30 mod. week 12	10 (55.6)	[32.7 ; 76.8]	2 (13.3)	[2.3 ; 37.5]	0.03
ACR50 week 12	9 (50)	[27.8 ; 72.2]	1 (6.7)	[0.3 ; 28.7]	0.01
ACR70 week 12	5 (27.8)	[11 ; 51.3]	0 (0)	[0 ; 21.8]	0.05
ACR90 week 12	2 (11.1)	[1.9 ; 32.1]	0 (0)	[0 ; 21.8]	0.49
EULAR Resp.	14 (77.8)	[54.7 ; 92.5]	7 (46.7)	[23.2 ; 71.3]	0.08
EULAR DAS(CRP) Resp.	13 (72.2)	[48.7 ; 89]	6 (40)	[18.1 ; 65.5]	0.09

Resp.: response, ACR20: ACR 20% response, and accordingly ACR30 to ACR90: ACR 30% response to ACR 90%response, ACR 30 mod.: modified ACR 30 response, EULAR response: good or moderate response according to the EULAR criterion based on DAS28(ESR) or if specified on DAS28(CRP), diff. response in %: difference between the response rates (in percent), 95% CI: 95% confidence interval

Figure S1: Response rates (PP)



P-values are shown above each pair of bars; P-values in red are significant
ACR, American College of Rheumatology; CRP, C-reactive protein; DAS, disease activity score; EULAR, European League Against Rheumatism; PP, per-protocol

Table S4: PP-Achievement of low disease activity (LDA), remission according to DAS28(ESR), DAS28(CRP), and extended remission based on DAS28(ESR)

	Canakinumab		**Placebo**		
Outcome parameter	**responder n (%)**	**95% CI**	**responder n (%)**	**95% CI**	**p value**
DAS28(ESR) LDA	6 (33.3)	[14.8 ; 56.9]	3 (20)	[5.4 ; 45.3]	0.46
DAS28(CRP) LDA	9 (50)	[27.8 ; 72.2]	2 (13.3)	[2.3 ; 37.5]	0.03
DAS28(ESR) remission	6 (33.3)	[14.8 ; 56.9]	0 (0)	[0 ; 21.8]	0.02
DAS28(CRP) remission	7 (38.9)	[18.9 ; 62.3]	0 (0)	[0 ; 21.8]	0.01
extended remission	5 (27.8)	[11 ; 51.3]	0 (0)	[0 ; 21.8]	0.05

(Column header “responder” describes the number of patients who have reached a low disease activity (LDA) or remission)

Table S5: PP - Comparison of the outcome at week 12 by ANCOVA for physician global, pain, 66/68 joint counts, HAQ-DI, n of joints with limitations of motion and SF-36

		Canakinumab outcome at week 12		Placebo outcome at week 12		Group compar.	
Parameter	**mean at scr. bl**	**LSmean**	**95% CI LSmean**	**LSmean**	**95% CI LSmean**	**p-value param.**	**p-value nonpar.**
Physician's global	5.4	3	[2 ; 4]	4.67	[3.6 ; 5.8]	0.03	.
Pain	5.7	3.63	[2.6 ; 4.7]	4.98	[3.8 ; 6.1]	0.09	.
66 SJC	6.9	3.51	[2 ; 5]	4.72	[3.1 ; 6.3]	.	0.04
68 TJC	9.9	5.38	[3.3 ; 7.5]	7.68	[5.4 ; 10]	.	0.01
Ferritin	669.5	483.5	[19 ; 948]	691.2	[182 ; 1201]	.	0.28
HAQ-DI	1.3	0.73	[0.5 ; 1]	1.13	[0.8 ; 1.4]	0.05	.
n of joints with LOM	5.6	5.89	[4.4 ; 7.4]	5.2	[3.5 ; 6.9]	0.54	0.60
SF-36 physical	29.1	40.03	[35.4 ; 44.7]	29.38	[24.3 ; 34.5]	0.01	.
SF-36 mental	42.4	46.64	[42.2 ; 51.1]	45.94	[41 ; 50.8]	0.84	.

66 SJC: 66 swollen joint count, 68 TJC: 68 tender joint count, Physician's global: Physician's global assessment of disease activity, Pain: Patient's assessment of pain in the joints, mean at scr. bl.: overall mean at screening and baseline (both groups) used for adjustment, obs.: observed, p-value param.: p-value of the parametric ANCOVA, p-nonpar: p-value of the nonparametric ANCOVA

Table S6: Response to different criteria and remission according to DAS28(ESR) of patients randomized to canakinumab (CAN) (n=18 patients) compared to placebo non-responder who switchted to canakinumab (n=7) by weeks treated with canakinumab

		Pat. random. to CAN (n=18)	Plac_NR who switched to CAN (n=7)	CAN vs Plac_NR
Response parameter	**weeks treated**	**responder n (%)**	**responder n (%)**	**diff. response in % [95% CI]**
DAS28(ESR)	4	11 (61.1)	6 (85.7)	-24·6 [-55.2 ; 21.3]
DAS28(ESR)	8	13 (72.2)	5 (71.4)	0·8 [-35 ; 44.2]
DAS28(ESR)	12	12 (66.7)	7 (100)	-33.3 [-59 ; 10.5]
DAS28(CRP)	4	12 (66.7)	4 (57.1)	9.5 [-31.2 ; 51.8]
DAS28(CRP)	8	14 (77.8)	5 (71.4)	6.3 [-29.1 ; 49.1]
DAS28(CRP)	12	12 (66.7)	3 (42.9)	23.8 [-21.2 ; 63.2]
EULAR Resp.	4	13 (72.2)	6 (85.7)	-13.5 [-44.2 ; 32.5]
EULAR Resp.	8	15 (83.3)	5 (71.4)	11.9 [-22.9 ; 53.9]
EULAR Resp.	12	14 (77.8)	7 (100)	-22.2 [-48. ; 21.2]
EULAR DAS(CRP) Resp.	4	12 (66.7)	5 (71.4)	-4.8 [-41 ; 40.4]
EULAR DAS(CRP) Resp.	8	17 (94.4)	6 (85.7)	8.7 [-18.1 ; 49.8]
EULAR DAS(CRP) Resp.	12	13 (72.2)	6 (85.7)	-13.5 [-44.2 ; 32.5]
ACR20	12	11 (61.1)	6 (85.7)	-24.6 [-55.2 ; 21.3]
ACR30	12	11 (61.1)	4 (57.1)	4 [-36.9 ; 46.7]
ACR30 mod.	12	10 (55.6)	4 (57.1)	-1.6 [-43.1 ; 43.2]
ACR50	12	9 (50)	4 (57.1)	-7.1 [-48.4 ; 37.9]
ACR70	12	5 (27.8)	2 (28.6)	-0.8 [-44.2 ; 35]
ACR90	12	2 (11.1)	2 (28.6)	-17.5 [-59 ; 16.4]
DAS28(ESR) remission	4	7 (38.9)	4 (57.1)	-18.3 [-58.4 ; 26.9]
DAS28(ESR) remission	8	7 (38.9)	3 (42.9)	-4 [-46.7 ; 36.9]
DAS28(ESR) remission	12	6 (33.3)	3 (42.9)	-9.5 [-51.8 ; 31.2]

SAE-Details

12-week double-blind period:

In a 36 year-old female patient, increased liver enzymes led to hospitalization. Since liver biopsy was consistent with drug-induced hepatotoxicity, all potentially causative drugs including canakinumab were stopped by the investigator and the laboratory values normalized subsequently. In a 51-year-old female patient, a patellofemoral pain syndrome led to hospitalization, but treatment with study drug continued without unblinding of the patient. In addition a patient was hospitalized at week 4 because of cerebral ischaemia. She was withdrawn due to this SAE. This patient was later diagnosed as having Whipple disease, being initially misdiagnosed as having AOSD. This patient developed at baseline a non-serious oral candidiasis. Since this patient did not suffer from AOSD, this SAE and this AE were excluded from the tables.

Second period (12-24 weeks)

In the group of patients treated with canakinumab a 30 years old male patient developed a deep vein thrombosis and a 66 years old female patient was hospitalized due to hypotonia. A 70 years old female patient treated with placebo developed 5 SAEs. She was hospitalized due to: fracture at MCP 5, hand fracture, removal of a medical device at MCP 5, upper abdominal pain, and acute cholecystis.

Suppl. Table S8 shows an overview of these SAEs.

LTE-period:

One event occurred in a 70 year-old patient due to hospitalization for upper abdominal pain (this patient had previously been hospitalized for cholecystitis in the 24-week blinded period). The patient was switched to canakinumab in the LTE phase and the study drug was only temporally suspended. The second SAE occurred in a 51years old female patient who developed a chondromalacia of the knee following a patello-femoral syndrome during the double blinded phase.

Table S7: Serious adverse events observed within the first 12-week-period and of the period from weeks 12 to 24

Exposure group	MedDRA preferred term	MedDRA SOC term	n of events	rate 100py	Hospita-lization	Severity	Ramifications for the investigational medicinal product
Canakinumab	Hepatotoxicity	Hepatobiliary disorders	1	6.5	yes	moderate	withdrawn
Canakinumab	Patellofemoral pain syndrome	Musculoskeletal and connective tissue disorders	1	6.5	yes	moderate	none
Canakinumab	Hypotonia	Nervous system disorders	1	6.5	yes	severe	none
Canakinumab	Deep vein thrombosis	Vascular disorders	1	6.5	no	moderate	none
Placebo	Abdominal pain upper	Gastrointestinal disorders	1	20.3	yes	severe	none
Placebo	Cholecystitis acute	Hepatobiliary disorders	1	20.3	yes	severe	none
Placebo	Fracture	Injury, poisoning and procedural complications	1	20.3	yes	severe	none
Placebo	Hand fracture	Injury, poisoning and procedural complications	1	20.3	yes	moderate	none
Placebo	Medical device removal	Surgical and medical procedures	1	20.3	yes	severe	none

Rate per 100py: rate per 100 patient-years.

AEs

Within the first 12 weeks period the exposure time to canakinumab of 18 patients randomized to the verum group and two patients who received one dose of canakinumab at week 4 summed up to 4.39 patient-years in total. Whereas the placebo exposure time of 17 patients randomized to placebo was 3.16 patient-years. During this very limited exposure time 47 non-serious adverse events were observed in patients exposed to canakinumab and 21 non-serious AE were observed during exposure to placebo. Among them, there were 6 patients who developed infections in both groups.

During the core study in total (between baseline and week 24) 27 patients were exposed to canakinumab: 18 patients randomized to canakinumab at baseline + 7 placebo non-responder who switched to canakinumab at week 12 plus 2 placebo patients who received canakinumab incorrectly at week 4. The exposure time of these 27 patients summarized to 15.3 patient-years. This exposure time was approximately 3 times higher than that of the 17 patients exposed to placebo: 4.9 patient-years. Due to the three-times higher exposure time the absolute number of AEs was higher in canakinumab exposed patients. However, the AE rate per 100 patient-years of exposure was rather equal in both groups. A summary of all AEs is shown in Table S9. Two placebo patients who dropped out in the first 10 days after baseline, one placebo responder and one placebo non-responder who switched to canakinumab did not experience an AE.

All patients who entered the LTE phase developed between one and 10 AEs during this phase. From the 33 AEs, 19 AEs were ongoing from the core phase of the study (Table S10).

Table S8: Non-serious adverse events observed within the core study from baseline to week 24

		Canakinumab				Placebo			
MedDRA SOC term	**MedDRA preferred term**	**n of AE**	**rate 100py**	**n of pat.**	**% of pat.**	**n of AE**	**rate 100py**	**n of pat.**	**% of pat.**
Blood and lymphatic system disorders	Lymphadenopathy	1	6.5	1	3.7	0	0	0	0
Ear and labyrinth disorders	Tinnitus	1	6.5	1	3.7	0	0	0	0
Endocrine disorders	Cushingoid	1	6.5	1	3.7	0	0	0	0
Eye disorders	Eyelid oedema	2	13.1	2	7.4	0	0	0	0
	Visual impairment	1	6.5	1	3.7	2	40.7	2	11.8
Gastrointestinal disorders	Abdominal pain	2	13.1	2	7.4	0	0	0	0
	Abdominal pain lower	1	6.5	1	3.7	0	0	0	0
	Aphthous ulcer	1	6.5	1	3.7	0	0	0	0
	Diarrhoea	2	13.1	2	7.4	2	40.7	2	11.8
	Nausea	4	26.1	3	11.1	1	20.3	1	5.9
General disorders and administration site conditions	Fatigue	1	6.5	1	3.7	2	40.7	2	11.8
	Influenza like illness	3	19.6	2	7.4	1	20.3	1	5.9
	Injection site rash	1	6.5	1	3.7	0	0	0	0
	Oedema peripheral	1	6.5	1	3.7	0	0	0	0
Infections and infestations	Bronchitis	2	13.1	2	7.4	1	20.3	1	5.9
	Erysipelas	1	6.5	1	3.7	0	0	0	0
	Herpes zoster	0	0	0	0	1	20.3	1	5.9

		Canakinumab				Placebo			
MedDRA SOC term	**MedDRA preferred term**	**n of AE**	**rate 100py**	**n of pat.**	**% of pat.**	**n of AE**	**rate 100py**	**n of pat.**	**% of pat.**
	Infection	1	6.5	1	3.7	0	0	0	0
	Nasopharyngitis	8	52.3	6	22.2	3	61	3	17.6
	Oral herpes	1	6.5	1	3.7	0	0	0	0
	Otitis media	1	6.5	1	3.7	0	0	0	0
	Pyrexia	1	6.5	1	3.7	0	0	0	0
	Rhinitis	1	6.5	1	3.7	0	0	0	0
	Tooth abscess	0	0	0	0	1	20.3	1	5.9
	Upper respiratory tract infection	1	6.5	1	3.7	0	0	0	0
	Urinary tract infection	0	0	0	0	1	20.3	1	5.9
Injury, poisoning and procedural complications	Meniscus injury	1	6.5	1	3.7	0	0	0	0
Investigations	Alanine aminotransferase increased	1	6.5	1	3.7	0	0	0	0
	Hepatic enzyme increased	2	13.1	2	7·4	0	0	0	0
	Transaminases increased	2	13.1	2	7.4	0	0	0	0
Metabolism and nutrition disorders	Appetite disorder	1	6.5	1	3.7	0	0	0	0
	Obesity	1	6.5	1	3.7	0	0	0	0
Musculoskeletal and connective tissue disorders	Arthralgia	7	45.7	4	14.8	1	20.3	1	5.9
	Back pain	1	6.5	1	3.7	0	0	0	0

		Canakinumab				Placebo			
MedDRA SOC term	**MedDRA preferred term**	**n of AE**	**rate 100py**	**n of pat.**	**% of pat.**	**n of AE**	**rate 100py**	**n of pat.**	**% of pat.**
	Groin pain	1	6.5	1	3.7	0	0	0	0
	Joint swelling	1	6.5	1	3.7	0	0	0	0
	Muscle spasms	0	0	0	0	1	20.3	1	5.9
	Osteoporosis	1	6.5	1	3.7	0	0	0	0
	Pain in extremity	1	6.5	1	3.7	0	0	0	0
	Still's disease	11	71.9	6	22.2	2	40.7	2	11.8
	Synovitis	1	6.5	1	3.7	0	0	0	0
	Tenosynovitis	1	6.5	1	3.7	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Anogenital warts	1	6.5	1	3.7	0	0	0	0
Nervous system disorders	Carpal tunnel syndrome	1	6.5	1	3.7	0	0	0	0
	Dizziness	1	6.5	1	3.7	0	0	0	0
	Headache	0	0	0	0	4	81.4	3	17.6
	Intercostal neuralgia	1	6.5	1	3.7	0	0	0	0
	Sciatica	1	6.5	1	3.7	0	0	0	0
Psychiatric disorders	Affect lability	1	6.5	1	3.7	0	0	0	0
Psychiatric disorders	Depression	0	0	0	0	1	20.3	1	5.9
	Hallucination	1	6.5	1	3.7	0	0	0	0

		Canakinumab				Placebo			
MedDRA SOC term	**MedDRA preferred term**	**n of AE**	**rate 100py**	**n of pat.**	**% of pat.**	**n of AE**	**rate 100py**	**n of pat.**	**% of pat.**
	Sleep disorder	1	6.5	1	3.7	1	20.3	1	5.9
Renal and urinary disorders	Dysuria	1	6.5	1	3.7	0	0	0	0
	Haematuria	1	6.5	1	3.7	0	0	0	0
	Micturition urgency	1	6.5	1	3.7	0	0	0	0
Reproductive system and breast disorders	Menstruation irregular	0	0	0	0	1	20.3	1	5.9
	Ovarian cyst	1	6.5	1	3.7	0	0	0	0
Respiratory, thoracic and mediastinal disorders	Pleurisy	0	0	0	0	0	0	0	0
	Rhinorrhoea	2	13.1	1	3.7	0	0	0	0
Skin and subcutaneous tissue disorders	Acne	1	6.5	1	3.7	0	0	0	0
	Alopecia	1	6.5	1	3.7	1	20.3	1	5.9
	Dermatitis allergic	0	0	0	0	1	20.3	1	5.9
	Nail dystrophy	1	6.5	1	3.7	0	0	0	0
	Pruritus	0	0	0	0	0	0	0	0
	Rash	1	6.5	1	3.7	1	20.3	1	5.9
	Rash pruritic	1	6.5	1	3.7	0	0	0	0
	Skin fissures	1	6.5	1	3.7	0	0	0	0
Vascular disorders	Fall	3	19.6	1	3.7	0	0	0	0

		Canakinumab				Placebo			
MedDRA SOC term	**MedDRA preferred term**	**n of AE**	**rate 100py**	**n of pat.**	**% of pat.**	**n of AE**	**rate 100py**	**n of pat.**	**% of pat.**
	Flushing	1	6.5	1	3.7	0	0	0	0
	Haematoma	2	13.1	2	7.4	0	0	0	0
total	total	98	640.1	26	96.3	29	590	13	76.5

N of AE: number of AEs, rate per 100py: rate per 100 patient-years, n(%) of pat.: number (%) of patients who experienced the AE, note: placebo patients who contributed also to canakinumab exposure were counted also there, therefore one canakinumab patient with an AE corresponded to 100*1/(18+2+7)=3.7%.

Table S9: Non-serious adverse events observed during the LTE phase

MedDRA SOC term	MedDRA preferred term	n of AE
Gastrointestinal disorders	Abdominal pain upper	1
General disorders and administration site conditions	Fatigue	1
	Influenza like illness	3
Hepatobiliary disorders	Primary biliary cholangitis	1
Infections and infestations	Gastrointestinal infection	1
	Hand-foot-and-mouth disease	1
	Infected bite	1
	Nasopharyngitis	6
	Periodontitis	1
	Pertussis	1
	Respiratory tract infection	1
	Upper respiratory tract infection	1
Injury, poisoning and procedural complications	Meniscus injury	1
Investigations	Gamma-glutamyltransferase increased	1
Musculoskeletal and connective tissue disorders	Myalgia	1
	Neck pain	1
	Pseudarthrosis	1
	Still's disease	2
Psychiatric disorders	Sleep disorder	1
Reproductive system and breast disorders	Vulva cyst	1
Respiratory, thoracic and mediastinal disorders	Asthma	2
	Cough	1
	Dysphonia	1
Skin and subcutaneous tissue disorders	Hyperhidrosis	1

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

EudraCT No. 2011-001027-20

Protocol version: 3.1

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

Date of the protocol: 20.10.2017

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Kedor C, *et al. Ann Rheum Dis* 2020; 79:1090–1097. doi: 10.1136/annrheumdis-2020-217155

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**t**i**ll'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	Approx. 14 study centres in Germany

centres:	
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.

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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).

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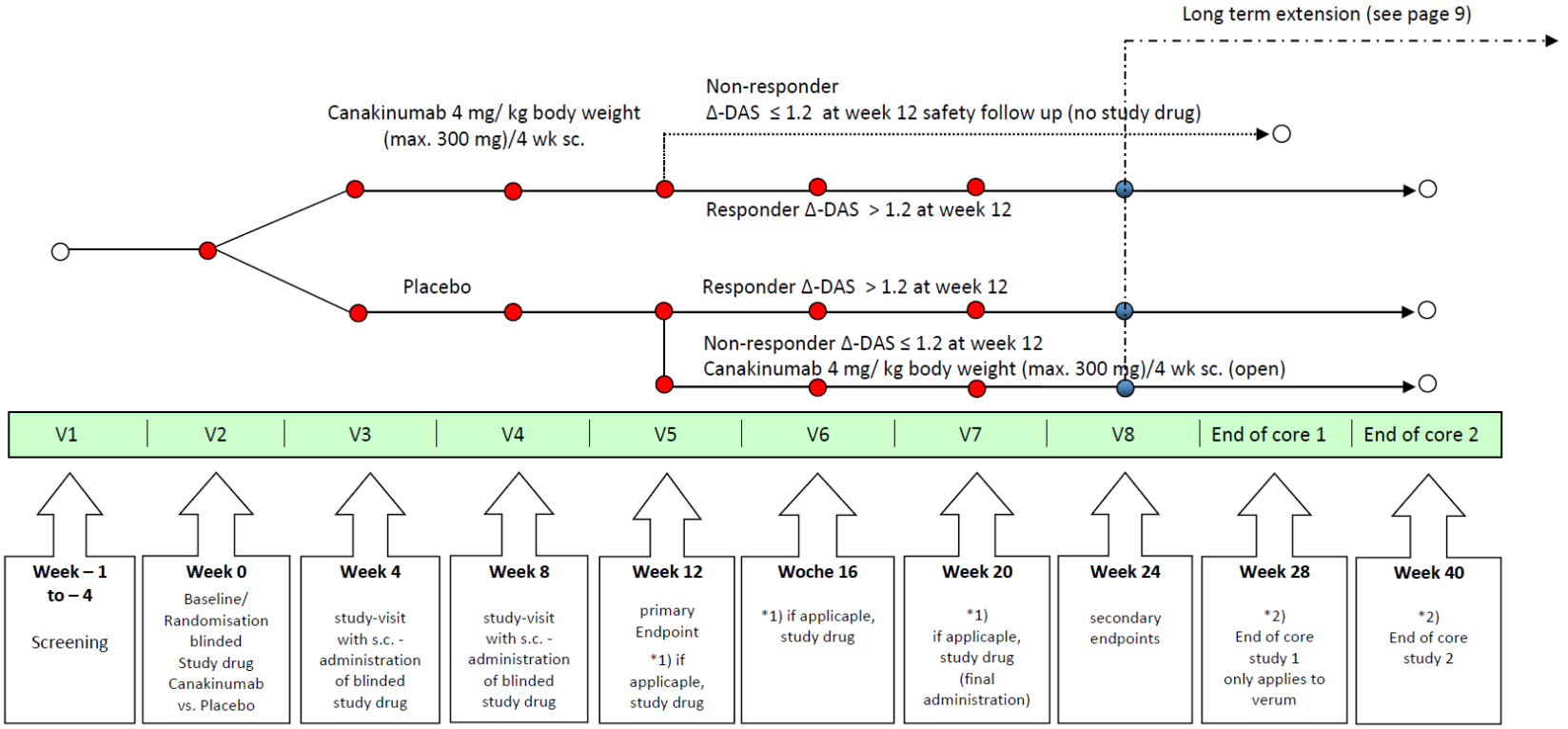
CONSIDER - Core Study procedures



*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

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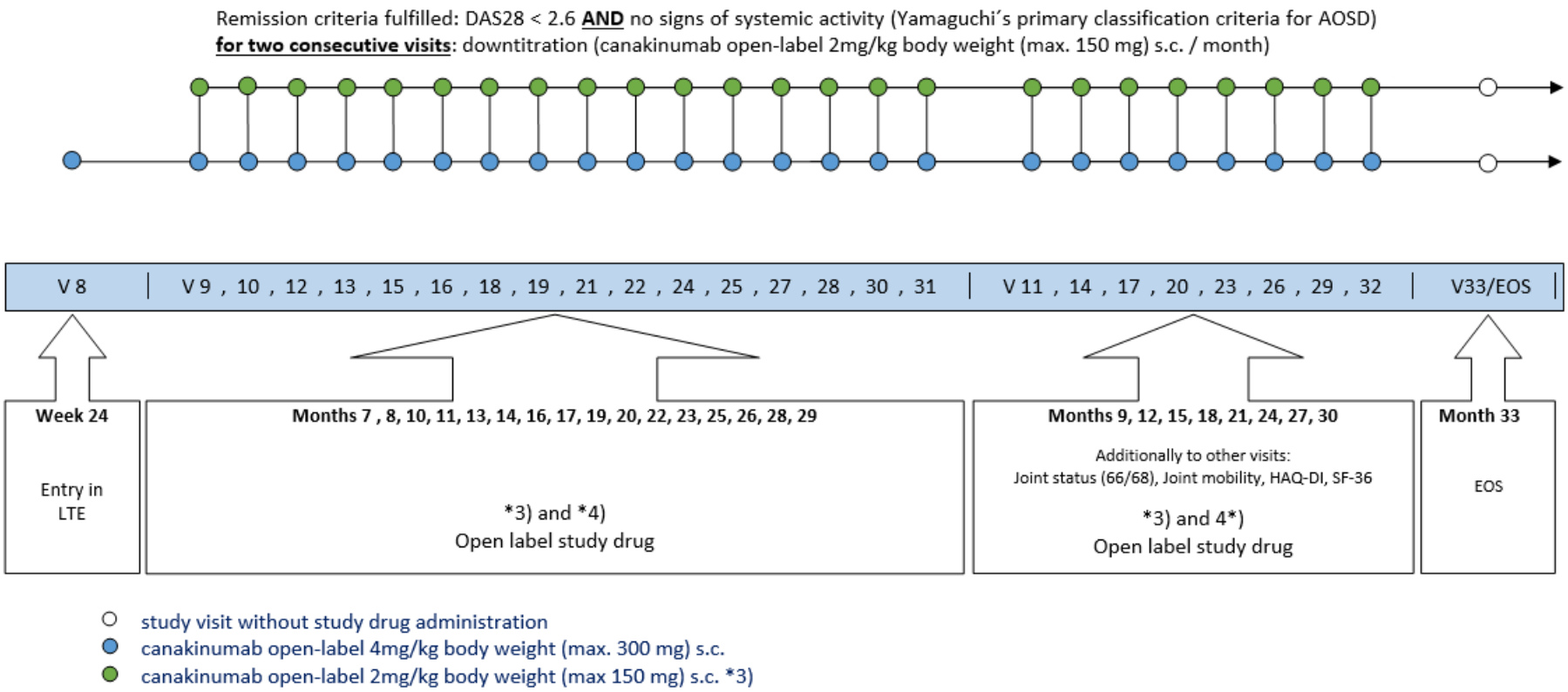
CONSIDER - LTE Study procedures



* 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.

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