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MCS110

Clinical Trial Protocol CMCS110X2201

A Phase II randomized, double-blind (Part A, B and C), placebo controlled (Part A and B only), study to assess safety, tolerability and efficacy of MCS110 on tumor size in patients with pigmented villonodular synovitis (PVNS)

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List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANCOVA	Analysis of Covariance
AUC	Area under the curve
BL	Baseline
BMD	Bone mineral density
BP	Blood pressure
bpm	beats per minute
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CK	Creatinine kinase
CK-MB	Creatinine kinase-MB
eCRF	(electronic) Case Report/Record Form
CPO	Country Pharma Organization
CR	Complete response
CRO	Contract Research Organization
CSF1	Colony stimulating factor
CSF-1R	Colony stimulating factor receptor
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTX-1	C-terminal Type I Collagen peptide

CMO&PS	Chief Medical Office & Patient Safety
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECM	Extracellular matrixEDC Electronic Data Capture
ELISA	enzyme-linked immunosorbent assay
EOS	End of Study
FACS	Fluorescence-Activated Cell Sorting
FDA	Food and Drug Administration

FOV	Field of view
GCTTS	Giant cell tumor of the tendon sheath
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
γ-GT	Gamma-glutamyl transferase
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HV	Healthy Volunteer
hsCRP	high sensitivity C-reactive protein
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICRO	Imaging CRO
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IL-6	Interleukin 6
IRB	Institutional Review Board
i.v.	Intravenous
IVRS / IWRS	Interactive Voice Response System / Interactive Web Response System
KOOS	Knee and Osteoarthritis Outcome Scale
LLOQ	Lower limit of quantification
LLN	Lower limit of normal
LR	Log Ratio
M-CSF	Macrophage colony-stimulating factor
MedRA	Medical Dictionary for Regulatory Activities
mm	Millimeters
MoA	Mode of action
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NOAEL	No-observable adverse effect level
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic

PK	Pharmacokinetic
p.o.	Per os
PoC	Proof of concept
PR	Partial response
PREE	Patient Rated Elbow Evaluation
PRO	Patient Reported Outcome
PVNS	Pigmented villonodular synovitis
RBC	Red blood cells
RECIST	Response evaluation criteria in solid tumors
RLP	Relapse
ROM	Range of motion
SAE	Serious adverse event
Scr	Screening
SD	Standard deviation
SNR	Signal to noise
SOP	Standard operating procedure
SPADI	Shoulder Pain and Disability Index
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
VAS	Visual analog scale
WBC	White blood cells
WHO	World Health Organization

Pharmacokinetic definitions and symbols

AUCinf	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
CL	The systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration [volume / time]
MRT	The mean residence time
T1/2	Half life
Tmax	The time to reach the maximum concentration after drug administration [time]
Vss	The volume of distribution at steady state following intravenous administration [volume]

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol).
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment.
Stop study participation	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug	Any drug administered to the subject as part of the required study procedures; includes investigational drug and any control drugs.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time-points.

Protocol synopsis

Title of study: A Phase II randomized, double-blind (Part A, B and C), placebo controlled (Part A and B only) study to assess safety, tolerability and efficacy of MCS110 on tumor size in patients with pigmented villonodular synovitis (PVNS).

Purpose and rationale:

Part A

This study is designed as a PoC (proof of concept) study of MCS110 in PVNS. The purpose of the present study is to measure the clinical response to MCS110 treatment in PVNS patients within 4 weeks after a single intravenous (i.v.) dose of 10 mg/kg of MCS110 using magnetic resonance imaging (MRI) to assess tumor volume, and to assess safety and tolerability in this patient population.

The study will also provide information on pharmacokinetic (PK) and pharmacodynamic (PD) effects of MCS110, including the assessment of hematological changes and measurement of biomarker responses of bone turnover. Corporate Confidential Information

The ultimate goal will be to assess whether treatment of PVNS with MCS110 can replace surgery, either in the primary or relapse setting. Thus, a multi-dose study Part B in PVNS is planned if the study Part A demonstrates PoC for M-CSF blockade in PVNS.

Part B

A single dose treatment with MCS110 has shown efficacy with an average reduction in tumor volume of 40% (29-50%). In order to better understand the longer-term tolerability and efficacy of MCS110, a multiple dose part is conducted (Part B). The ultimate goal of this portion of the study will now be to assess whether treatment of PVNS or GCTTS with multiple doses of MCS110 can lead to a complete tumor ablation and thus replace surgery, either in the primary or relapse setting.

Part C

With the aims/goals to achieve maximum tumor volume reduction and tumor cell eradication and be as safe as possible it appears most appropriate to explore the efficacy and safety of MCS110 at doses lower than 10 mg/kg. In Part C of the study it will be tested whether repeated administration of doses lower than 10 mg/kg MCS110 may have the same efficacy as multiple doses of 10 mg/kg of MCS110 while simultaneously showing improved AE profile. In addition to tumor volume reduction efficacy will be assessed by reduction of metabolic activity Corporate Confidential and on the tumor tissue level Corporate Confidential Information

Objectives:

Primary objectives:

Part A

- To assess efficacy of a single i.v. dose of MCS110 in reducing the size of PVNS tumors over 4 weeks evaluated by volume of PVNS lesion by MRI.
- To assess safety and tolerability of MCS110 in this population.

Part B/C

- To assess efficacy of multiple doses of MCS110 in reducing the size of PVNS or GCTTS tumors 8 weeks following the last dose evaluated by volume of PVNS or GCTTS lesion by MRI.
- To assess safety and tolerability of MCS110 in this population.

Key secondary objectives:

Part A and Part B and C

- To characterize the PK of single (Part A) and multiple doses (Part B) of MCS110 in PVNS or GCTTS (GCTTS only in Part B) patients.
- To assess total M-CSF circulating levels in PVNS or GCTTS (GCTTS only in Part B and C) patients.
- To assess the mode of action of MCS110 by measuring serum C-terminal Type I Collagen peptide (CTX-I), a biomarker of bone resorption.
- To assess the immunogenicity of MCS110 in this population.
- To assess the duration of clinical response, if any, by joint range of motion.
- To assess the degree of functional recovery using questionnaires.

Part B/C

- To assess joint pain using a visual analog scale (VAS).
- To assess time to surgery.
- To assess time to relapse (based on MRI).

Study design Part A:

A randomized, double-blind, placebo controlled study with 2 arms; MCS110 or placebo.

Study design Part B:

A randomized, double-blind, placebo controlled study with 2 arms; MCS110 or placebo followed by MCS110 single arm, open label part.

Study design Part C:

A randomized, double-blind study with 3 parallel arms (3 mg/kg, 5 mg/kg, and 10 mg/kg of MCS110).

Population Part A:

The study population will be comprised of males and females aged 18 years or older with diagnosis of PVNS, who had no more than two surgeries. A total of up to 12 patients will be enrolled to participate in the study.

Population Part B:

The study population will be comprised of males and females aged 18 years or older with diagnosis of PVNS or GCTTS with an evaluable tumor size by MRI.

Population Part C:

The study population will be comprised of males and females aged 12 years or older with diagnosis of PVNS or GCTTS with an evaluable tumor size by MRI.

Inclusion/Exclusion criteria:

For full inclusion / exclusion please see Section 4.

Key Inclusion:

Part A

- Men and women aged ≥ 18 years with diagnosis of PVNS, who have at least one measurable site of disease on MRI and are expected to undergo surgery, will be eligible to participate in the study.

Part B

- Men and women aged ≥ 18 years with diagnosis of PVNS or GCTTS, who have at least one measurable site of disease on MRI, will be eligible to participate in the study.

Part C

- Men and women aged ≥ 12 years with diagnosis of PVNS or GCTTS, who have at least one measurable site of disease on MRI, will be eligible to participate in the study.
  Adolescents (≥ 12, <18 years old) eligible for enrollment need to have (1) symptomatic disease for which surgical intervention is indicated and the surgical procedure itself would be associated with significant morbidity, or (2) recurrent disease.

Key Exclusions:

Part A

- Patients with PVNS, who have had more than two operations on the affected joint (not including diagnostic biopsies) or have received chemotherapy or radiation therapy to treat PVNS. Previous operations to a different joint from the one now being treated are not exclusionary.

Part B and Part C

- Patients with PVNS or GCTTS whose tumor is not evaluable by MRI, in the judgment of the central MRI reading site.

Parts A, B and C

- Patients who have undergone major surgery ≤ three (3) months prior to starting study drug or who have not recovered from side effects of such therapy. Any systemic illness that precludes definitive surgery for PVNS, or increases the risk to patients due to potential immunosuppression.
- Use of any intra-articularly administered drug (to the joint affected by PVNS) within 4 weeks prior to dosing.
- Patients with elevated troponin T and creatinine kinase (CK) levels (> 1.5 x ULN for the laboratory) at the screening and/ or baseline.
- Patients with dermal change indicative of lymphedema, or phlebolymphedema; specifically, any trace thickening, faint discoloration, swelling or obscuration of anatomic architecture on close inspection suggesting edema. In addition there must be no pitting edema at any site, particularly the head (periorbital), neck, trunk, genital and visceral areas.
- Patients, who are currently receiving immunosuppressive treatment, including systemic corticosteroids greater than the equivalent of 10 mg of prednisone, which cannot be discontinued at least 4 weeks prior to starting study drug.
- Patients engaged in or planning to enter a resistance exercise training program.

Investigational and reference therapy:

Part A and Part B:

- Patients will be assigned to one of the following 2 treatment arms in a ratio of 2:1 MCS110 to placebo.

Part C:

- Patients will be assigned to one of the following treatment arms of MCS110: 3 mg/kg, 5 mg/kg or 10 mg/kg MCS110 in a ratio of about 2:2:1 with the option of a further extension of the efficient lower dose arm.

Efficacy / pharmacodynamic assessments:

- Tumor volume measurement by MRI assessment
- Total M-CSF in plasma and synovial fluid
- Mode of action biomarkers Corporate Confidential Information
- Joint range of motion
- Specific joint questionnaires and VAS for pain evaluation (only in Part B and C)

Safety assessments:

- Physical exam
- Vital signs
- Height and weight
- ECG
- Hematology
- Clinical chemistry
- Analysis of immunoglobulins
- Glomerular filtration rate
- Coagulation parameters
- Muscle enzymes
- Urinalysis
- Pregnancy test
- Adverse Events

Pharmacokinetic assessments:

- PK blood for MCS110
- PK blood for Total M-CSF
- Immunogenicity of MCS110

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Data analysis:

Part A

The tumor size (volume) as assessed by MRI technique will be the primary measure of efficacy in this study. The tumor size at baseline and after 4 weeks will be log transformed. The log ratio (LR) to baseline of the tumor size (change from baseline of log transformed volume) will be the primary endpoint.

A Bayesian analysis of the primary endpoint will be carried out after each patient complete the 4-week treatment period, and the PoC criterion, as defined below, will be evaluated. At least 3 patients (2 on active and one on placebo) must be included in the analysis to declare a positive PoC.

The PoC criterion is two-fold, as follows:

- Prob(LR(treated) < LR(placebo)) > 0.90; i.e., 90% confidence in superiority to placebo
- Prob(LR(treated) - LR(placebo) < log(0.6)) > 0.50; i.e., 50% confidence in the treated group ratio being 40% below the placebo group ratio

Part B

The tumor volume will continue to be the primary measure of efficacy. In particular, if the tumor is too small to be measurable, it is considered as complete response.

Tumor volumes will be listed and descriptively summarized at each MRI assessment time by treatment groups (treatment group 1 = MCS110 throughout the trial, treatment group 2 = Placebo for the first dose and MCS110 from the second dose) accordingly. Moreover, the number and percentage of patients with complete tumor response will be presented, and the time that the complete tumor response is observed will be listed by patient and treatment group.

In addition, we may pool treatment groups by matching the 1st dose of MCS110 in treatment group 1 to the 2nd dose (1st of MCS110) in treatment group 2. More specifically, for treatment group 2, the measurement right before patients receiving the first dose of MCS110 (2nd dose from screening) will be treated as the new baseline and assessment time-points will be adjusted accordingly.

Part C

The tumor volume will continue to be the primary measure of efficacy. In particular, if the tumor is too small to be measurable, it is considered as complete response.

Tumor volumes will be listed and descriptively summarized at each MRI assessment time by MCS110 dose group (3 mg/kg, 5 mg/kg, and 10 mg/kg). Moreover, the number and percentage of patients with complete tumor response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) based on RECIST criteria will be presented, and the time that the complete tumor response is observed will be listed by patient and dose group.

Tumor volume reduction after 3 doses will guide the decision on whether to continue the lower dose levels of 3 or 5 mg/kg MCS110 with the initial dosing (3 mg/kg or 5 mg/kg) or increase the dosing to 10 mg/kg for the 3 following doses. The decision criteria for the 10 mg/kg arm will remain the same as in Part B.

If a lower dose (3 mg/kg or 5 mg/kg) is well tolerated and shows the same efficacy as 10 mg/kg defined as a tumor volume reduction of at least 45%, evaluated by week 12 MRI after patient received 3 MCS110 doses, then three additional MCS110 doses of the same dose will be administered to the patient. Additional patients may be enrolled in this lower dose group in open label to extend the efficacious arm up to approximately 10 patients.

Assessment Schedule (Part A)

	Screening	Baseline	Treatment													EoS
Visit Numbers [1]	*1*	*2*	*3*						*4*	*5*	*6*	*7*	*8*	*9*	*10*	*777*
Weeks	-	-	1						2	4	5	6	8	12	18	24
Study Day	- 28 to - 8	- 7 to - 1	1						15	28	33	43	57	85	127	169
Time hrs	-	-	pre	0	1	2	3	5	-	-	-	-	-	-	-	-
Informed consent	X															
Inclusion / Exclusion criteria	X	X														
Relevant med. hist. / Current med. cond.	X	X														
Demography	X															
Prior / concomitant medication(s)	X															
Hepatitis B and C screen and HIV screen	X															
Quantiferon TB test	X															
Alcohol test, drug screen	X	X														
FSH test (females only)	X															
Pregnancy test (in serum, females only)	X	X							X	X		X	X			X
Physical examination (incl. index joint ROM)	X	X							X	X			X			X
Body height	X															
Body weight	X	X							X	X			X			X
Vital Signs: Body temperature, Blood pressure, Pulse	X	X	X	X[2]		X			X	X	X		X	X	X	X
ECG evaluation [3]	X	X	X			X				X			X			X
Hematology and Clinical chemistry	X	X							X	X		X	X	X	X	X
Urinalysis	X	X							X	X		X	X			X
Drug administration (MCS infusion)[4]				X												
Surgery											X					
MRI	X[5]									X						
QoL, General Health Status, WOMAC Questionnaires		X							X	X			X			X
Corporate Confidential Information	X	X							X	X			X	X	X	X
PK blood(for MCS110) [7]			X		X[8]	X	X	X[8]	X	X	X	X	X	X	X	X
PK blood (for Total M-CSF)		X	X					X[8]	X	X	X	X	X	X	X	X
Corporate Confidential Information											X					
	X	X						X	X	X			X	X	X	X
	X	X							X	X			X	X	X	X
	X	X							X	X			X		X	
	X	X							X	X			X	X	X	X
		X							X	X			X	X	X	X
		X							X	X			X	X	X	X
Corporate Confidential Information		X														
											X					
	X	X							X	X			X	X	X	X
SAE reporting [9]	X															
Adverse Event reporting[10]			X													
Study completion information																X
Comments	as required															

[1] Visit structure given for internal programming purpose only.

[2] Vital signs will be monitored every 15 minutes (± 5 minutes) during the infusion.

[3] During the study 12-lead ECG's should be conducted prior to blood collection.

[4] Dosing should occur within 8 days of validated reference MRI, infusion duration 1hr +/- 10 mns.

[5] Two sequencial MRIs will be carried out at this visit.

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[7] PK Blood for MCS110 : sampling 5 minutes after end of infusion.

[8] These samples are not required to be taken fasting.

[9] SAE reporting from time of signing informed consent until 30 days after subject has stopped study participation.

[10] AEs to be reported from time of first study drug administration on Day 1 until study completion.

Assessment Schedule (Part B)

CMCS110X2201 Part B - Assessment Schedule

	Screening	Baseline	Treatment																				
Visit Numbers [1]	*1*	*2*	*3*					*4*	*5*					*6*						*7*			
Weeks	-	-	1					2	4					8						12			
Months									1					2						3			
Study Day	- 28 to - 8	- 7 to - 1	1					15	29					57						85			
Time hrs	-	-	pre	0	1	2	5	-	pre	0	1	2	5	pre	0	1	2	3	5	pre	0	1	2	5
Informed consent	X																						
Inclusion / Exclusion criteria	X	X																					
Relevant med. hist. / Current med. cond.	X	X																					
Demography	X																						
Prior / concomitant medication(s)	X																						
Hepatitis B and C screen and HIV screen	X																						
Quantiferon TB test	X																						
Alcohol test, drug screen	X	X[11]							X					X						X			
FSH test (females only)	X																						
Pregnancy test (in serum, females only)	X	X[11]						X	X					X						X			
Physical examination	X	X						X	X					X						X			
Joint Range Of Motion	X	X						X	X					X						X			
Body height	X																						
Body weight	X	X						X	X					X						X			
Vital Signs: Body temperature, Blood pressure, Pulse	X	X	X	X[2]	X	X		X	X	X[2]	X	X		X	X[2]	X		X		X	X[2]	X	X
ECG evaluation [3]	X	X	X		X			X	X		X			X		X				X		X	
Hematology and Clinical chemistry [15]	X	X[11]						X	X					X						X			
Urinalysis	X	X[11]						X	X					X						X			
Drug administration (MCS110 infusion)[4,17,18]				X						X					X						X[16]		
MRI	X[5]								X					X						X			
Corporate Confidential Information	X[13]																						
	X								X														
VAS Pain Evaluation	X	X						X	X					X						X			
EQ5D, mHAQ and joint specific questionnaires (KOOS, SPADI or PREE)	X	X						X	X					X						X			
Corporate Confidential Information	X		X						X					X						X			
PK blood (for MCS110) [7]			X		X[8]		X[8]	X	X		X[8]		X[8]	X		X[8]			X[8]	X		X[8]		X[8]
PK blood (for Total M-CSF)		X	X				X[8]	X	X				X[8]	X					X[8]	X				X[8]
Biopsy [12]																							
Corporate Confidential Information																							
	X	X						X	X					X						X			
	X	X						X	X					X						X			
		X						X	X					X						X			
		X																					
	X	X	X					X	X					X						X			
SAE reporting [9]	X																						
Adverse Event reporting [10]			X																				
Study completion information																							
Comments	as required																						

[1] Visit structure given for internal programming purpose only.

[2] Vital signs will be monitored every 15 minutes (± 5 minutes) during the infusion.

[3] During the study 12-lead ECG's should be conducted prior to blood collection.

[4] Dosing should occur within 8 days after site received MRI validation from the vendor, infusion duration 1hr +/- 10 mns.

[5] Two sequencial MRIs will be carried out at this visit.

Corporate Confidential Information

[7] PK Blood for MCS110: All post-dose samples to be taken after end of infusion. The "1 hr" time point should be taken immediately after the end of infusion.

[8] These samples are not required to be taken fasting.

[9] SAE reporting from time of signing informed consent until 30 days after subject has stopped study participation.

[10] AEs to be reported from time of first study drug administration on Day 1 until study completion.

[11] Alcohol and drug screen, pregnancy test, hematology and clinical chemistry : screening results can be used at baseline if baseline is planned in the next 7 days following screening.

Corporate Confidential Information

[15] Hematology and clinical chemistry for safety purpose will be analyzed locally before any dosing day. Any other visits saftey samples will be analyzed by the central lab

[16] At week 12, after dosing, patient's treamtment will be unblinded.
If Day 1 treatment is placebo, Assessment Schedule B1 will be applied from the next visit.
If Day 1 treatment is MCS110, Assessment Schedule B2 will be applied from the next visit.

Corporate Confidential Information

[18] For Part B1 patients, an unscheduled visit 8 should be planned 4 weeks after visit 8 (week 20) as administration day of dose 5.
For Part B2 patients, an unscheduled visit 7 should be planned 4 weeks after visit 7 (week 16) as administration day of dose 5.

[19] Collection of these samples is discontinued as of 30-Aug-2016

Corporate Confidential Information

Assessment Schedule (Part B1 – Applicable if Day 1 dose is placebo)

Part B 1 - If double-blind Dose day 1 = placebo

	Treatment					Treatment					Treatment					Follow-up							EoS
Visit Numbers [1]	*8*					*8 UNS1* [17,18]					*8 UNS2* [17,18]					*9*	*10*	*11*	*12*	*13*	*14*	*15*	*777*
Visit Numbers for programming purposes [1]	*108*					*116*					*117*					*109* [20]	*110*	*111*	*112*	*113*	*114*	*115*	*778*
Weeks	16					20					24					24	28	40	52	64	76	88	100
Months	4					5					6					6	7	10	12	16	19	22	25
Study Day	112					141					169					169	196	-	-	-	-	-	-
Time hrs	pre	0	1	2	5	pre	0	1	2	5	pre	0	1	2	5	-	-	-	-	-	-	-	-
Informed consent																							
Inclusion / Exclusion criteria																							
Relevant med. hist. / Current med. cond.																							
Demography																							
Prior / concomitant medication(s)	X																						
Hepatitis B and C screen and HIV screen																							
Quantiferon TB test																							
Alcohol test, drug screen	X					X					X												
FSH test (females only)																							
Pregnancy test (In serum, females only)	X					X					X						X						X
Physical examination	X					X					X						X						X
Joint Range Of Motion	X					X					X					X	X	X	X	X	X	X	X
Body height																							
Body weight	X					X					X						X		X		X		X
Vital Signs: Body temperature, Blood pressure, Pulse	X	X [2]		X	X	X	X [2]		X	X	X	X [2]		X	X	X	X	X	X	X	X	X	X	X
ECG evaluation [3]	X			X		X			X		X			X			X	X	X	X	X	X	X	X
Hematology and Clinical chemistry [15]	X					X					X					X	X	X	X	X	X	X	X
Urinalysis	X					X					X						X	X	X	X	X	X	X
Drug administration (MCS110 infusion) [4,17,18]		X					X [17, 18]					X [17,18]											
MRI	X					X					X					X	X	X	X	X	X	X	X
																			X			X [14]	
																X							
	X					X					X					X	X	X	X	X	X	X	X
	X					X					X					X	X	X	X	X	X	X	X
	X					X					X					X	X	X	X	X	X	X	X
	X		X [8]		X [8]	X		X [8]		X [8]	X		X [8]		X [8]	X	X	X	X	X	X	X	X
	X				X [8]	X				X [8]	X				X [8]	X	X	X	X	X	X	X	X
	X					X					X					X	X	X	X	X	X	X	X
	X					X					X					X	X	X	X	X	X	X	X
	X					X					X					X	X	X	X	X	X	X	X
	X					X					X					X	X	X	X	X	X	X	X
SAE reporting [9]	X																						
Adverse Event reporting [10]	X																						
Study completion information																							X
Comments	X																						

Assessment Schedule (Part B2 – Applicable if Day 1 dose is MCS110)

Part B 2 - If double-blind Dose day 1 = MCS110

	Treatment					Treatment					Follow-up							EoS
Visit Numbers [1]	*7 UNS1* [17,18]					*7 UNS2* [17,18]					*8*	*9*	*10*	*11*	*12*	*13*	*14*	*777*
Visit Numbers for programming purposes [1]	*215*					*216*					*208* [21]	*209*	*210*	*211*	*212*	*213*	*214*	*779*
Weeks	16					20					20	24	36	48	60	72	84	96
Months	4					5					5	6	9	12	15	18	21	24
Study Day	113					141					141	169	-	-	-	-	-	-
Time hrs	pre	0	1	2	5	pre	0	1	2	5	-	-	-	-	-	-	-	-
Informed consent																		
Inclusion / Exclusion criteria																		
Relevant med. hist. / Current med. cond.																		
Demography																		
Prior / concomitant medication(s)	X																	
Hepatitis B and C screen and HIV screen																		
Quantiferon TB test																		
Alcohol test, drug screen	X					X												
FSH test (females only)																		
Pregnancy test (in serum, females only)	X					X						X						X
Physical examination	X					X						X						X
Joint Range Of Motion	X					X					X	X	X	X	X	X	X	X
Body height																		
Body weight	X					X						X		X		X		X
Vital Signs: Body temperature, Blood pressure, Pulse	X	X [2]		X	X	X	X [2]		X	X	X	X	X	X	X	X	X	X
ECG evaluation [3]	X			X		X			X			X	X	X	X	X	X	X
Hematology and Clinical chemistry [15]	X					X					X	X	X	X	X	X	X	X
Urinalysis	X					X						X	X	X	X	X	X	X
Drug administration (MCS110 infusion) [4, 17,18]		**X** [17,18]					**X** [17,18]											
MRI	X					X					X	X	X	X	X	X	X	X
														X			X [14]	
											X							
	X					X					X	X	X	X	X	X	X	X
	X					X					X	X	X	X	X	X	X	X
	X					X					X	X	X	X	X	X	X	X
	X		X [8]		X [8]	X		X [8]		X [8]	X	X	X	X	X	X	X	X
	X				X [8]	X				X [8]	X	X	X	X	X	X	X	X
	X					X					X	X	X	X	X	X	X	X
	X					X					X	X	X	X	X	X	X	X
	X					X					X	X	X	X	X	X	X	X
	X					X					X	X	X	X	X	X	X	X
SAE reporting [9]	X																	
Adverse Event reporting [10]	X																	
Study completion information																		X
Comments	X																	

Assessment schedule Part B1 and B2

[1] Visit structure given for internal programming purpose only.
[2] Vital signs will be monitored every 15 minutes (± 5 minutes) during the infusion.
[3] During the study 12-lead ECG's should be conducted prior to blood collection.
[4] Dosing should occur within 8 days after site received MRI validation from the vendor, infusion duration 1hr +/- 10 mns.
[5] Two sequencial MRIs will be carried out at this visit.

[7] PK Blood for MCS110: All post-dose samples to be taken after end of infusion. The "1 hr" time point should be taken immediately after the end of infusion.
[8] These samples are not required to be taken fasting.
[9] SAE reporting from time of signing informed consent until 30 days after subject has stopped study participation.
[10] AEs to be reported from time of first study drug administration on Day 1 until study completion.
[11] Alcohol and drug screen, pregnancy test, hematology and clinical chemistry : screening results can be used at baseline if baseline is planned in the next 7 days following screening.

[15] Hematology and clinical chemistry for safety purpose will be analyzed locally before any dosing day. Any other visits saftey samples will be analyzed by the central lab
[16] At week 12, after dosing, patient's treamtment will be unblinded.
If Day 1 treatment is placebo, Assessment Schedule B1 will be applied from the next visit.
If Day 1 treatment is MCS110, Assessment Schedule B2 will be applied from the next visit

[18] For Part B1 patients, an unscheduled visit 8 should be planned 4 weeks after visit 8 (week 20) as administration day of dose 5.
For Part B2 patients, an unscheduled visit 7 should be planned 4 weeks after visit 7 (week 16) as administration day of dose 5.
[19] Collection of these samples is discontinued as of 30-Aug-2016
[20] Visit 109 (Part B1) will not be performed if patients had visits optional dosing visits 116 and 117 (schedule B1)
[21] Visit 208 (Part B2) will not be performed if patients had visits optional dosing visits 215 and 216 (schedule B2).

Assessment Schedule (Part B – re-dosing)

	RLP	redosing Screening	Redosing Treatment									Redosing Follow-up visit			EoS
Visit Numbers	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12 (optional)* [19]	*777*
Visit Numbers for Cmed Programming [1]	*301*	*302*	*303*	*304*	*305*	*306*	*307*	*308*	*309*	*310*	*311*	*312 (optional)* [13]	*780*
Weeks	-	-	1	2	4	8	12	16	20	24	36	48	60
Months					1	2	3	4	5	6	9	12	15
Study Day	-	-7	1	15	29	57	85	113	141	169	253	337	421
Time hrs	-	-	pre 0 1 2 5	-	pre 0 1 2 5	pre 0 1 2 5	pre 0 1 2 5	pre 0 1 2 5	pre 0 1 2 5	-	-	-	-
Informed consent	X												
Inclusion / Exclusion criteria		X											
Relevant med. hist. / Current med. cond.													
Demography													
Prior / concomitant medication(s)	X												
Hepatitis B and C screen and HIV screen		X											
Quantiferon TB test		X											
Alcohol test, drug screen		X			X	X	X	X	X				
FSH test (females only)		X											
Pregnancy test (in serum, females only)		X		X	X	X	X	X	X				X
Physical examination		X		X	X	X	X	X	X				X
Joint Range Of Motion		X		X	X	X	X	X	X	X	X	X	X
Body height		X											
Body weight		X		X	X	X	X	X	X	X	X	X	X
Vital Signs: Body temperature, Blood pressure, Pulse		X	X X^2 X X	X	X X^2 X X	X X^2 X X	X X^2 X X	X X^2 X X	X X^2 X X	X	X	X	X
ECG evaluation [3]		X	X X	X	X X	X X	X X	X X	X X	X	X	X	X
Hematology and Clinical chemistry [4]		X		X	X	X	X	X	X	X	X	X	X
Urinalysis		X		X	X	X	X	X	X	X	X	X	X
Drug administration (MCS110 infusion)[5,6,7]			X		X	X	X	X	X				
MRI [12]				X	X	X	X	X	X	X	X	X	X
Corporate Confidential Information											X		
		X		X									
		X		X	X	X	X	X	X	X	X	X	X
		X		X	X	X	X	X	X	X	X	X	X
										X	X	X	X
										X	X	X	X
										X	X	X	X
										X	X	X	X
										X	X	X	X
SAE reporting[10]	X												
Adverse Event reporting[11]	X												
Study completion information													X
Comments	as required												

[1] Visit structure given for internal and vendors programming purpose only.

[2] Vital signs will be monitored every 15 minutes (+ 5 minutes) during the infusion

Corporate Confidential Information

[3] Hematology and clinical chemistry for safety purpose will be analyzed locally before any dosing day. Any other visits safety samples will be analyzed by the central lab.
Lab parameters list: section 6.5.4 of the protocol.

[5] Infusion duration 1hr +/- 10 minutes.

Corporate Confidential Information

[7] After the last follow-up visit at which the relapse was confirmed, the patient will undergo a Redosing Screening for safety purposes, and if eligible, Redosing visits (303, 304, etc.)
After the last redosing visit, the patient will restart the follow-up visits from the point where they were interrupted by the redosing.
The first follow-up visit should occurr 1 month after the last redosing. The follow-up should last at least 6 months after the last dose received.
Unscheduled follow-up visits can be performed, so the follow-up lasts at least 6 months after the last dose received.

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[10] SAE reporting from time of signing informed consent until 30 days after subject has stopped study participation.

[11] AEs to be reported from time of first study drug administration on Day 1 until study completion.

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[13] Redosing Follow-up Visit 312 is mandatory for patients who enetered the redosing cycle before completing the V12 in the follow-up after the first course of the treatment.
Unscheduled follow-up visits can be performed, so the follow-up lasts at least 6 months after the last dose received.

Assessment Schedule (Part C – Adults) Protocol Amendment 07

Patients who completed visit 14 or 15 by the time Protocol Amendment 07 is approved, need to come back to the site within 1 month for an end of study visit to perform remaining assessments

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Patients who did not yet achieve visit 14 or 15 by the time Protocol Amendment 07 is approved, need to follow Protocol Amendment 07 assessment schedule.

CMCS110X2201 Part C - Assessment Schedule

	Screening	Baseline	Treatment																										Follow-up				EoS
Visit Numbers [1]	*1*	*2*	*3*				*4*	*5*					*6*				*7*				*8*				*9*				*10*	*11*	*12*	*13*	*777*
Weeks	-	-	1				2	4					8				12				16				20				24	28	40	56	72
Months	-1						1						2				3				4				5				6	7	10	14	18
Study Day	- 28 to -22	-21 to -8	- 7 to - 1				1						15				29				57				85				113				141				169	197	281	393	505
Allowed visit window (days)	-	-	-				-						±3				±3				±5				±5				±5				±5				±5	±8	±8	±8	±8
Time hrs	-	-	-	pre	0	1	2	5	-	pre	0	1	2	5	pre	0	1	2	5	pre	0	1	2	5	pre	0	1	2	5	pre	0	1	2	5	pre	0	1	2	5	-	-	-	-	-
Informed consent	X																																											
Inclusion / Exclusion criteria	X	X																																										
Relevant med. hist. / Current med. cond.	X	X																																										
Demography	X																																										
Prior / concomitant medication(s)																		X																										
Hepatitis B and C screen and HIV screen	X																																										
Quantiferon TB test	X																																										
Alcohol test, drug screen	X		X[11]						X					X						X					X						X											
FSH test (females only)	X																																										
Pregnancy test (in serum, females only)	X																																										X
Pregnancy test (urine, females only)			X[11]					X	X					X						X					X					X	X											
Physical examination	X		X					X	X					X						X					X					X	X	X	X	X								
Joint Range Of Motion	X		X					X	X					X						X					X					X	X	X	X	X								
Body height	X																																										
Body weight	X		X					X	X					X						X					X					X	X	X	X	X								
Vital Signs: Body temperature, Blood pressure, Pulse	X		X	X	X[2]	X	X	X	X	X[2]	X	X	X	X[2]	X	X	X	X[2]	X	X	X	X[2]	X	X	X	X[2]	X	X	X	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG evaluation [3]	X		X	X		X		X	X		X			X		X				X			X			X				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and Clinical chemistry [13]	X		X[11]					X	X					X						X					X					X	X	X	X	X								
Urinalysis	X		X[11]					X	X					X						X					X					X	X	X	X	X								
Drug administration (MCS110 infusion) [14, 15]					**X**					**X**					**X**				**X**[14]				**X**[15]				**X**															
MRI [4]		X							X				X[16]				X[16]				X[16]				X[16]						X	X	X[16]	X									
Corporate Confidential Information		X[5]																																X	X[17]								
			X																																								
	X		X					X	X					X						X					X					X	X	X	X	X								
	X		X					X	X					X						X					X					X	X	X	X	X								
	X			X					X					X						X					X					X	X	X	X	X								
				X		X[6]		X	X		X[6]		X[6]		X[6]		X[6]		X[6]		X		X[6]		X		X[6]		X	X	X	X	X								
			X	X		X[6]		X	X		X[6]		X[6]		X[6]		X[6]		X[6]		X		X[6]		X		X[6]		X	X	X	X	X								
			X																												X											
			X																												X											
	X		X					X	X					X						X					X					X	X	X	X	X								
			X																												X		X		X							
			X																												X											
	X		X	X				X	X					X			X			X					X					X	X	X	X	X								
SAE reporting [9]																	X																											
Adverse Event reporting [9]																	X																											
Study completion information																																											X
Comments	as required																																										

Corporate Confidential Information

Assessment Schedule (Part C – Adults) Protocol Amendment 06

As a number of patients complete the study according to Protocol Amendment 06 –before Protocol Amendment 07 is approved - this assessment schedule is therefore being kept below.

CMCS110X2201 Part C - Assessment Schedule

	Screening		Baseline	Treatment																												Follow-up						EOS
Visit Numbers [1]	*1*		*2*	*3*				*4*	*5*					*6*					*7*					*8*					*9*					*10*	*11*	*12*	*13*	*14*	*15*	*777*
Weeks	-		-	1				2	4					8					12					16					20					24	28	40	56	72	88	104
Months	-1							1						2					3					4					5					6	7	10	14	18	22	26
Study Day	-28 to -22	-21 to -8	-7 to -1	1				15	29					57					85					113					141					169	197	281	393	505	617	729
Allowed visit window (days)	-	-	-	-				±3	±3					±5					±5					±5					±5					±5	±8	±8	±8	±8	±8	±8
Time hrs	-	-	-	pre	0	1	2	5	-	pre	0	1	2	5	pre	0	1	2	5	pre	0	1	2	5	pre	0	1	2	5	pre	0	1	2	5	-	-	-	-	-	-	-
Informed consent	X																																							
Inclusion / Exclusion criteria	X		X																																					
Relevant med. hist. / Current med. cond.	X		X																																					
Demography	X																																							
Prior / concomitant medication(s)	X																																							
Hepatitis B and C screen and HIV screen	X																																							
Quantiferon TB test	X																																							
Alcohol test, drug screen	X		X[11]						X					X					X					X					X						X						
FSH test (females only)	X																																							
Pregnancy test (in serum, females only)	X																																							X
Pregnancy test (urine, females only)			X[11]					X	X					X					X					X					X					X	X						
Physical examination	X		X					X	X					X					X					X					X					X	X	X	X	X	X	X
Joint Range Of Motion	X		X					X	X					X					X					X					X					X	X	X	X	X	X	X
Body height	X																																							
Body weight	X		X					X	X					X					X					X					X					X	X	X	X	X	X	X
Vital Signs: Body temperature, Blood pressure, Pulse	X		X	X		X[2]	X	X	X		X[2]	X	X	X		X[2]	X	X	X		X[2]	X	X	X		X[2]	X	X	X		X[2]	X	X	X	X	X	X	X	X
ECG evaluation [3]	X		X	X			X		X			X		X			X		X			X		X			X		X			X		X	X	X	X	X	X	X
Hematology and Clinical chemistry [13]	X		X[11]					X	X					X					X					X					X					X	X	X	X	X	X	X
Urinalysis	X		X[11]					X	X					X					X					X					X					X	X	X	X	X	X	X
Drug administration (MCS110 infusion)[14, 15]					**X**					**X**					**X**					**X[14]**					**X[19]**					**X**										
MRI [4]		X							X					X[16]					X[16]					X[16]					X[16]					X	X	X[16]	X	X[16]	X	X
		X[5]																																			X				X[17]
			X																																	X					
	X		X					X	X					X					X					X					X					X	X	X	X	X	X	X
	X		X					X	X					X					X					X					X					X	X	X	X	X	X	X
	X			X					X					X					X					X					X					X	X	X	X	X	X	X
				X		X[6]		X[6]	X		X[6]		X[6]	X		X[6]		X[6]	X		X[6]		X[6]	X		X[6]		X[6]	X		X[6]		X[6]	X	X	X	X	X	X	X
			X	X			X[6]		X			X[6]		X			X[6]		X			X[6]		X			X[6]		X			X[6]		X	X	X	X	X	X	X
			X																																	X					
			X																																		X					
	X		X					X	X					X					X					X					X					X	X	X	X	X	X	X
			X																X																	X		X			X
			X																																		X					
			X																																		X					
	X		X	X				X	X					X					X					X					X					X	X	X	X	X	X	X
SAE reporting [9]	X																																								
Adverse Event reporting [9]	X																																								
Study completion information																																									X
Comments	as required																																								

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Assessment Schedule (Part C - Adolescent patients)

CMCS110X2201 Part C - Adolescents Assessment Schedule

	Screening		Baseline	Treatment																						Follow-Up				EoS
Visit Numbers [1]	*1*		*2*	*3*			*4*	*5*				*6*				*7*				*8*				*9*			*10*	*11*	*12*	*13*	*777*
Weeks	-		-	**1**			**2**	**4**				**8**				**12**				**16**				**20**			24	**28**	40	56	72
Months	-1			1				2				3				4				5							6	**7**	10	14	18
Study Day	-28 to -15	-14 to -8	-7 to -1	1			15	29				57				85				113				141			169	**197**	281	393	505
Allowed visit window (days)	-	-	-	-			±3	±3				±5				±5				±5				±5			±5	**±8**	±8	±8	±8
Time hrs	-	-	-	pre	0	1	2	5	-	pre	0	1	2	5	pre	0	1	2	5	pre	0	1	2	5	pre	0	1	2	5					
Informed consent	X																														
Inclusion / Exclusion criteria	X		X																												
Relevant med. hist. / Current med. cond.	X		X																												
Demography	X																														
Prior / concomitant medication(s)																X															
Hepatitis B and C screen and HIV screen [15]	X																														
Tuberculosis PPD skin test	X																														
Alcohol test, drug screen		X						X				X				X				X				X				**X**			
Pregnancy test (in serum, females only)		X																													X
Pregnancy test (urine, females only)			X				X	X				X				X				X				X			X	**X**			
Physical examination	X		X				X	X				X				X				X				X			X	**X**	X	X	X
Joint Range Of Motion	X		X				X	X				X				X				X				X			X	**X**	X	X	X
Body height	X																														
Body weight	X		X				X	X				X				X				X				X			X	**X**	X	X	X
Vital Signs: Body temperature, Blood pressure, Pulse	X		X	X	X [2]	X	X	X	X	X [2]	X	X	X	X [2]	X	X	X	X	X [2]	X	X	X	X [2]	X	X	X	X	**X**	X	X	X
ECG evaluation [3]	X		X	X		X	X	X		X		X	X		X	X		X		X		X		X		X		**X**	X	X	X
Hematology and Clinical chemistry [12]		X		X			X	X				X				X				X				X				**X**	X	X	X
Urinalysis		X					X	X				X				X				X				X				**X**	X	X	X
Drug administration (MCS110 infusion) [13, 14]					**X**				**X**				**X**				**X** [13]				**X** [14]				**X**						
MRI [4]	X							X								X [10]				X								**X**	X	X [16]	X
Corporate Confidential Information			X																											X	X [5]
	X		X				X	X				X				X				X				X			X	**X**	X	X	X
	X		X				X	X				X				X				X				X			X	**X**	X	X	X
				X												X												**X**	X		X
				X	X [5]											X	X [6]				X [5]	X [5]		X [5]			X	**X**	X		X
				X	X [5]												X [6]					X [5]					X	**X**			X
			X																										**X**			
			X																										**X**			
		X		X				X				X				X				X				X			X	**X**	X	X	X
			X																										**X**			
																																X
SAE reporting [9]	X																														
Adverse Event reporting [9]	X																														
Study completion information																															X
Comments	as required																														

[1] Visit structure given for internal programming and vendors programming purpose only.
[2] Vital signs will be monitored every 15 minutes (± 5 minutes) during the infusion.
[3] During the study 12-lead ECG's should be conducted prior to blood collection

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Assessment Schedule (Part C – re-dosing)

CMCS110X2201 Part C - Redosing Assessment Schedule

	Relapse diagnosis (RLP)	Redosing Screening [2]	Redosing Treatment																												Redosing Follow-up			EoS
Visit Numbers [1]	1	2	3					4	5				6					7				8				9					10	11	12 [9]	777
Visit Numbers for Cmed Programming [1]	401	402	403					404	405				406					407				408				409					410	411	412 [9]	781
Weeks	-	-	1					2	4				8					12				16				20					28	40	56	72
Months	-	-1						1					2					3				4				5					6	10	14	18
Study Day	-	-7 to -1	1					15	29				57					85				113				141					169	281	393	505
Allowed visit window (days)	-	-	-					±3	±3				±5					±5				±5				±5					±6	±8	±8	±8
Time hrs	-	-	pre	0	1	2	5	-	pre	0	1	2	5	pre	0	1	2	5	pre	0	1	2	5	pre	0	1	2	5	pre	0	1	2	5	-	-	-	-
Informed consent	X																																			
Inclusion / Exclusion criteria		X																																		
Relevant med. hist. / Current med. cond.		X																																		
Prior / concomitant medication(s)																		X																		
Hepatitis B and C screen and HIV screen [13]		X																																		
Tuberculosis test [14]		X																																		
Alcohol test, drug screen		X							X				X					X				X				X										
FSH test (females ≥18 years only)		X																																		
Pregnancy test (in serum, females only)		X																																		X
Pregnancy test (urine, females only)								X	X				X					X				X				X					X					
Physical examination		X						X	X				X					X				X				X					X	X	X	X		
Joint Range Of Motion		X						X	X				X					X				X				X					X	X	X	X		
Body height		X																																		
Body weight		X						X	X				X					X				X				X					X	X	X	X		
Vital Signs: Body temperature, Blood pressure, Pulse		X	X		X [5]	X	X	X	X		X [5]	X	X	X		X [5]	X	X	X		X [5]	X	X	X		X [5]	X	X	X		X	X	X	X		
ECG evaluation [3]		X	X			X		X	X			X		X				X				X				X					X	X	X	X		
Hematology and Clinical chemistry [4]		X						X	X				X					X				X				X					X	X	X	X		
Urinalysis		X						X	X				X					X				X				X					X	X	X	X		
Drug administration (MCS110 infusion) [6]				X						X					X					X					X [6]						X					
MRI [7, 12]									X									X					X									X			X	X	X
																																				X [10]
		X						X	X				X					X				X				X					X	X	X	X		
		X						X	X				X					X				X				X					X	X	X	X		
			X						X				X					X								X					X	X	X	X [15]		
			X		X [16]				X				X		X [16]			X		X [16]				X [19]	X [19]	X		X [19]			X	X	X	X [15]		
			X		X [16]				X				X		X [19]			X		X [19]				X [19]	X [19]	X		X [19]			X	X	X	X [15]		
																																			X	X	X	X
																																			X [15]			X [15]
																																						X [15]
			X [15]						X [15]				X [15]		X [15]			X [15]				X [15]				X [15]					X [15]	X [15]	X [15]	X [15]
SAE reporting [8]															X																					
Adverse Event reporting [8]															X																					
Study completion information																																				X
Comments			as required																																	

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1 Introduction

1.1 Background

MCS110 is a high-affinity, humanized, monoclonal antibody (IgG1/κ) directed against human macrophage colony-stimulating factor (M-CSF; also known as colony-stimulating factor-1 (CSF-1)). In cell-based assays, MCS110 blocks the ability of human M-CSF to activate the M-CSF receptor, (CSF-1R or *c-fms*), which is mediating the functions of M-CSF. M-CSF is the primary regulator of the survival, proliferation, differentiation and function of mononuclear phagocytes (monocytes, microglia and osteoclasts). It also is involved in a wide range of biological activities including reproduction (Cohen et al 1999) and lipid metabolism (Watanabe et al 1995). There are a number of inflammatory disorders that display elevated levels of M-CSF including atherosclerosis, where M-CSF is known to be present in atherosclerotic lesions and may contribute to plaque progression (Shaposhnik et al 2010).

M-CSF is also thought to play a key role in a rare synovial tumor, pigmented villonodular synovitis (PVNS), in which a part or all of the synovial lining of a joint or tendon sheath [called giant cell tumor of the tendon sheath (GCTTS)] proliferates to form outgrowths varying from a single nodular thickening to a mass of villi which can occupy the whole joint cavity. PVNS occurs mainly in young otherwise healthy adults and affects equally females and males between 20 and 50 years. It is a slowly growing tumor which is diagnosed by MRI with a mean delay before diagnosis of about 3 years (Ottaviani et al 2011). PVNS is locally aggressive, with the capacity to invade surrounding soft tissues and bone, erode the articular cartilage and eventually cause significant morbidity. The knee and hip are most commonly involved. No approved pharmacological intervention is available to date to treat PVNS. Current treatment of PVNS requires surgery, either surgical excision of localized PVNS or synovectomy for diffuse PVNS. Patients with diffuse disease can have multiple recurrences and bulky disease that result in significant bone destruction.

Synovial tissue in PVNS is highly vascular and characterized by extensive hemosiderin deposition and the presence of numerous macrophages and osteoclast-like giant cells (Murphey et al 2008; Fiocco et al 2010). In most cases of PVNS a disease specific *COL6A3-CSF1* translocation is detectable in a distinct subpopulation of tumor cells (West et al 2006; Cupp et al 2007). The presence of high levels of M-CSF expression, recruiting a large body of macrophages to the tumor site, appears to be a consistent feature in all forms of this disease.

This hypothesis, that tumor-derived M-CSF is causative for the recruitment of macrophages into the synovia, drives the rationale for evaluating M-CSF blockade for PVNS treatment, which could provide an adjunct or alternative to surgical interventions. Treatment with MCS110 could block M-CSF activity emanating from the tumor and consequently block tumor growth, reducing synovitis and ultimately bone lesion occurrence and size. Recent preclinical work in a novel renal subcapsular xenograft model of PVNS demonstrated that an anti-M-CSF monoclonal antibody significantly inhibits host macrophage infiltration into this tumor with the number of macrophages being reduced by more than 50%. Macrophage infiltration is the main contribution to tumor growth (Cheng et al 2010).

Imatinib, (Gleevec®), a tyrosine kinase inhibitor that suppresses the growth of chronic myeloid leukemia progenitor cells has been reported to partially block the M-CSF receptor at therapeutic concentrations (Dewar et al 2005). It has been shown in one case report that treatment with imatinib resulted in a complete remission of a PVNS tumor (Blay et al 2008).

The present study is a proof of concept (PoC) study, which aims to investigate the efficacy of MCS110 in the treatment of PVNS by reducing tumor size. Based on the data shown in a preclinical model with an anti M-CSF antibody (Cheng et al 2010) we hypothesized, with the study design of X2201 Part A, that tumor volume can be reduced by at least 40% with a single dose of 10 mg/kg MCS110. This was considered a clinically meaningful reduction, which should facilitate curative surgery. Corporate Confidential Information

Therefore, it was initially decided to continue the study with up to 4 monthly doses of 10 mg/kg MCS110, which is extended to 6 monthly doses in agreement with FDA

This dosing extension increases the chance to eliminate the tumor. Thus, in the future, pharmacological treatment of PVNS with MCS110 may help not only to delay but even may avoid synovectomy. Corporate Confidential Information

MRI, because of its superior soft-tissue contrast and its use of non-ionizing radiation, is the preferred modality for diagnosing PVNS, and facilitates differentiating it from other synovial proliferative processes. Tumor size has been well established in clinical trials as an independent predictor of response to radiation therapy (Grossman et al 1973; Perez et al 1992). With the 3-D imaging capability of MRI, volumetric changes can be measured and may be a more sensitive assessment of treatment efficacy than one-dimensional assessment, as demonstrated in studies in patients with cervical cancer (Mayr et al 2006) and breast cancer (Partridge et al 2005).

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Study CMCS110A2101

Study CMCS110A2101 was a first-in-human study conducted in patients with asymptomatic castrate-resistant prostate cancer with bone metastases. This study, designed to establish the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of MCS110 administered as an i.v. infusion, was terminated after completion of the first dose level cohort due to slow enrollment and strategic re-positioning of this program for new indications. A total of 3 patients were enrolled and treated with 0.01 mg/kg; all 3 patients completed the planned 3 cycles of study treatment. The investigator did not suspect observed adverse events to be related to MCS110 aside from one patient who experienced an infusion related reaction characterized by transient CTCAE (Common Terminology Criteria for Adverse Events) grade 1 (mild) chills, grade 2 (moderate) hypotension, and grade 2 (moderate) dizziness 1 hour after completing the first MCS110 infusion. All 3 adverse events resolved approximately 1 hour after occurrence. The patient received i.v. fluids for supportive care. No infusion related reactions were noted following the subsequent MCS110 infusions for this patient. The 2 additional patients treated with MCS110 did not experience infusion related reactions. Corporate Confidential Information

Study CMCS110X2201

The total number of patients with PVNS exposed to MCS110 in Part A, B and C of this study is 36 (7 patients in Part A, 11 in Part B and 18 patients in Part C). In Part B and C patients received multiple doses of either 10 mg/kg in Part B or 3, 5, or 10 mg/kg in Part C. During the study eleven serious adverse events (SAEs) were reported, four of them were considered study drug related and occurred in the ongoing Part C:

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1.3.1 Human pharmacokinetic and immunogenicity data

Study CMCS110A2101

The pharmacokinetics of MCS110 were studied in 3 patients with prostate cancer receiving 0.01 mg/kg in study CMCS110A2101administered as an i.v. infusion once every 2 weeks with a total of 6 doses for each patient [MCS110 Investigator Brochure].

1.4 Study purpose

This study was designed originally as a proof of concept study of MCS110 in PVNS. The purpose of the study (Part A) was to measure the clinical response to MCS110 treatment in diagnosed PVNS patients within 4 weeks after a single i.v. dose of 10 mg/kg using MRI to assess tumor volume, and to assess safety and tolerability in this patient population.

Part A also provided information on pharmacokinetic and pharmacodynamic effects of MCS110, including the assessment of hematological changes and measurement of biomarker responses of bone turnover. Corporate Confidential Information

The goal of Part B was to assess whether treatment of PVNS with multiple doses of MCS110 can lead to complete tumor ablation. If successful, the use of MCS110 as an alternative to surgery in PVNS, either in the primary or relapse setting, will be considered.

In Part B repeated dosing (3 doses) of PVNS patients with 10 mg/kg MCS110 resulted in an average tumor volume reduction of about 50%. In Part C we will test whether repeated administration of doses lower than 10 mg/kg MCS110 may have the same efficacy as multiple doses of 10 mg/kg of MCS110 while simultaneously showing improved AE profile. In addition to tumor volume reduction, efficacy will be assessed by determining changes in metabolic activity and on the tumor tissue level (biopsy) Corporate Confidential Information

2 Study objectives

2.1 Primary objectives Part A

- To assess efficacy of a single i.v. dose of MCS110 in reducing the size of PVNS tumors compared to placebo over 4 weeks evaluated by volume of PVNS lesion by MRI.
- To assess safety and tolerability of MCS110 in this population.

2.2 Secondary objectives Part A

- To characterize the pharmacokinetics of a single dose of MCS110 in PVNS patients.
- To assess pharmacodynamic effects of MCS110 on:
  - total circulating M-CSF levels in PVNS patients.
  - the soluble form of M-CSFR (sCSF-1R).
  - serum C-terminal Type I Collagen peptide (CTX-I), a biomarker of bone resorption.
  - circulating CD14+ monocytes and CD14+CD16+ monocytes in blood by FACS.
- To assess the immunogenicity of MCS110 in this population.
- To assess the duration of clinical response, if any, by joint range of motion.
- To assess the degree of functional recovery at time points according to Assessment Schedule.

2.4 Primary objectives Part B

- To assess efficacy of multiple i.v. doses of MCS110 in reducing the volume of PVNS or GCCTS tumors evaluated by MRI after 8 weeks post last dose.
- To assess safety and tolerability of multiple i.v. doses of MCS110 in this population.

2.5 Secondary objectives Part B

- To characterize the pharmacokinetics of multiple doses of MCS110 in PVNS or GCTTS patients.
- To assess pharmacodynamic effects of MCS110 on:
  - total circulating M-CSF levels in PVNS or GCTTS patients.
  - the soluble form of M-CSFR (sCSF-1R).
  - serum C-terminal Type I Collagen peptide (CTX-I), a biomarker of bone resorption.
- To assess the immunogenicity of MCS110 in this population.
- To assess the duration of clinical response, if any, by joint range of motion
- To assess the degree of functional recovery (questionnaires EQ5D, mHAQ, and joint specific questionnaire KOOS [Knee and Osteoarthritis Outcome Scale], SPADI [Shoulder Pain and Disability Index] and PREE [Patient Rated Elbow Evaluation]).
- To assess joint pain using a visual analog scale (VAS).
- To assess time to surgery.
- To assess time to relapse (based on MRI).

2.7 Primary objectives Part C

- To assess efficacy of multiple doses of 3 mg/kg, 5 mg/kg and 10 mg/kg MCS110 in reducing the size of PVNS or GCTTS tumors after 8 weeks following the last dose evaluated by volume of PVNS or GCTTS lesion by MRI.
- To assess safety and tolerability of MCS110 in this population.

2.8 Secondary objectives Part C

- To characterize the PK of multiple doses of MCS110 in PVNS or GCTTS patients.
- To assess pharmacodynamic effects of MCS110 on:
  - total circulating M-CSF levels in PVNS or GCTTS patients.
  - serum C-terminal Type I Collagen peptide (CTX-I), a biomarker of bone resorption.
- To assess the immunogenicity of MCS110 in this population.
- To assess the duration of clinical response, if any, by joint range of motion.
- To assess the degree of functional recovery using questionnaires.
- To assess joint pain using a visual analog scale (VAS).
- To assess time to surgery.
- To assess time to relapse (based on MRI).

3 Investigational Plan

3.1 Part A

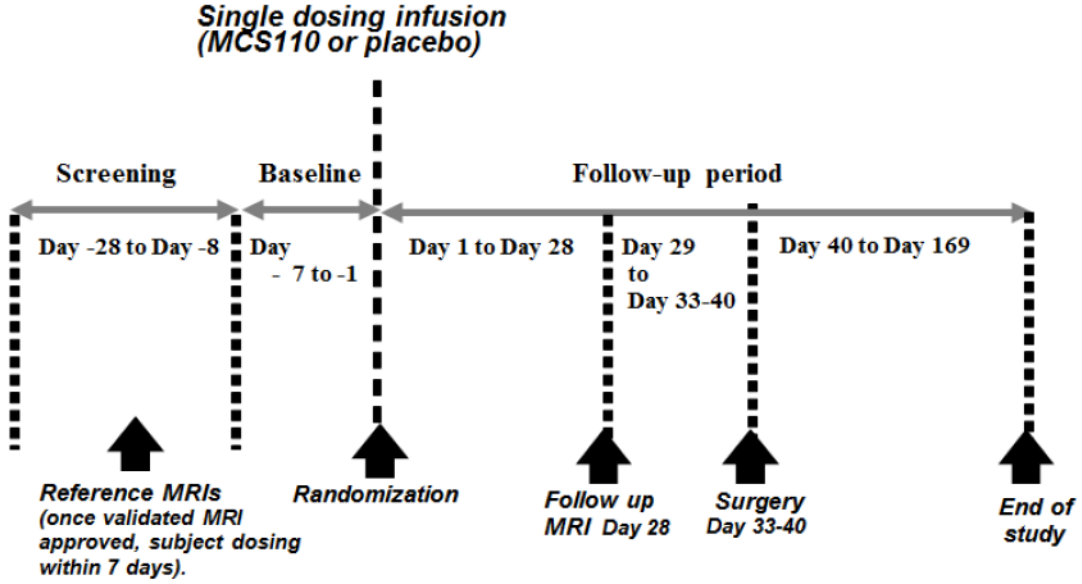
3.1.1 Study design Part A

The study is a randomized, double-blind, placebo-controlled, parallel-arm, single dose exploratory PoC clinical trial with 2:1 randomization of MCS110 to placebo. Enrollment will proceed until up to 12 evaluable patients have been recruited, where "evaluable" is defined as completing the protocol through surgery (approximately day 33). Patients diagnosed with PVNS, who are awaiting surgery, will be treated with a single i.v. dose of 10 mg/kg of MCS110. Patients will only be eligible for the study, if they have at least one tumor site that can be measured by MRI. MRI of PVNS provides unique features depicting the extent of the tumor, synovial proliferation, joint effusion, bone erosion and deposits of hemosiderin (Cheng et al 2004; Steinbach et al 1989; Frick et al 2007; Murphey et al 2008).

The primary outcome of tumor shrinkage will be determined by MRI at 4 weeks, followed by surgery to remove residual tumor and to provide histological evidence of tumor cellularity. Patients will be monitored over a period of approximately 6 months to evaluate safety and tolerability of MCS110 and for relapse.

Patients who meet the eligibility criteria at screening will be admitted to baseline evaluations. All baseline safety evaluation results must be available prior to dosing. Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis) adverse event and serious adverse event monitoring. This study will be carried out primarily in the out-patient setting. However, during the period around the surgery it is expected that patients may be hospitalized as part of routine clinical care, at the discretion of the treating physician. However, no research procedures will require inpatient admission *per se*.

Figure 3-1 Study design Part A



3.1.2 Rationale for study design Part A

The proposed study is a double-blind, parallel-arm study of up to 12 evaluable patients with PVNS, with a 2:1 active to placebo ratio treatment assignment. PVNS appears to be driven by excessive M-CSF production, the target of MCS110 and thus provides a direct biological test of the potential efficacy of MCS110 in binding its target and producing an important biological and medical effect by shrinking the tumor. As there is no approved drug available today to treat PVNS, current treatment of PVNS always requires surgery. This includes either surgical excision of localized PVNS or synovectomy for diffuse PVNS.

The study will be performed in PVNS patients who are scheduled for surgery. After diagnosis and assessment of tumor volume by MRI, patients will receive either a single i.v. dose of MCS110 or placebo and the effect of treatment on tumor size will be assessed 4 weeks later by MRI just before surgery.

MRI assessment provides an objective, non-invasive method to analyze tumor size. The time period between final diagnosis of PVNS and surgery is generally around 4 weeks, so participation in this study will not significantly extend this time period. This is especially important for placebo treated patients to keep tumor growth minimal and avoid progressive symptoms. Four weeks is also a short time considering that the mean delay before diagnosis often is 2-3 years (Ottaviani et al 2011). Placebo treated patients will be included as there is currently no medical standard of care to compare to. Several outcomes are based on patient cooperation or a self-report (joint range of motion score) and placebo will help to reduce bias.

Although there is currently no information available on short-term disease progression in PVNS, tumor growth is expected to be minimal within 4 weeks (<10%). Patients will be randomized in a 2:1 ratio of active versus placebo to keep the number of placebo treated patients as low as possible, but allow assessment of active treated versus placebo treated patients.

3.2 Part B and C

3.2.1 Study Design Part B

The study CMCS110X2201 Part B is a randomized, double-blind, placebo-controlled, parallel-arm, exploratory PoC clinical trial with 2:1 randomization of MCS110 to placebo for the first dose followed by open-label multiple doses. Part B first dose will be administered double-blind, placebo-controlled. All patients will receive active treatment after the first dose and the study will continue as an open label study.

Day 1 blinding will be maintained until week 12, which corresponds to the fourth dose for the potential Day 1 MCS110 patients. After patient reaches week 12 (Visit 7), Day 1 treatment received by the patient will be un-blinded in order to allow Day 1 placebo patients to receive a fourth dose of MCS110.

If patient received placebo at Day 1, then, the patient will follow Assessment Schedule Part B1 after Visit 7.

If patient received MCS110 at Day 1, then, the patient will follow Assessment Schedule Part B2 after Visit 7.

In the multiple dose Part B patients receive up to 4 doses of 10 mg/kg MCS110 administered once every 4 weeks. Two additional MCS110 doses will be administered, if MCS110 is well tolerated and if a reduction in tumor volume of >50% can be demonstrated after the 3rd MCS110 dose by MRI taken before the 4th dose.

The primary outcome of Part B of the study will be tumor volume after multiple doses of MCS110 monitored by MRI. The primary outcome will be assessed 8 weeks after the last dose of MCS110, a time point, where free drug is expected to decline rapidly, based on modeling and simulations of free MCS110 concentrations.

Patients who meet the eligibility criteria at screening will be admitted to baseline evaluations. All baseline safety evaluation results must be available prior to dosing. Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis) adverse event and serious adverse event monitoring. This study will be carried out primarily in the out-patient setting.

In order to monitor the duration of the tumor size reducing effect of MCS110, patients will have follow-up visits every 3 months for up to 2 years to document changes in growth of the residual tumor or to detect recurring tumor by MRI. The time intervals of 3 months are according to the standard of care for patients, who had undergone surgery.

In case of relapse or regrowth of residual PVNS tumor during the follow-up period, patients will be offered to start another treatment course once the previous MCS110 treatment was longer than 6 months ago (Figure 3-3), then the patient will follow Assessment Schedule Part B re-dosing. At any time during the study, investigator and/or patient can decide to undergo surgery if patient's PVNS conditions require such a treatment.

Total enrollment in the study (Part A and Part B) will proceed until up to 18 evaluable patients have been recruited, where Part B "evaluable" patient is defined as completing the protocol until at least 2 doses of MCS110 were administered and a follow-up MRI was performed. Patients will only be eligible for the study, if they have at least one tumor site that can be measured by MRI. MRI of PVNS provides unique features depicting the extent of the tumor, synovial proliferation, joint effusion, bone erosion and deposits of hemosiderin (Cheng et al 2004; Steinbach et al 1989; Frick et al 2007; Murphey et al 2008). Part A is completed, seven patients received a single dose of MCS110 or placebo. In the multiple dose Part B, patients can be treated with up to 6 doses of MCS110 following IRB approval of the amended protocol CMCS110X2201-v04.

Figure 3-2 Study design Part B

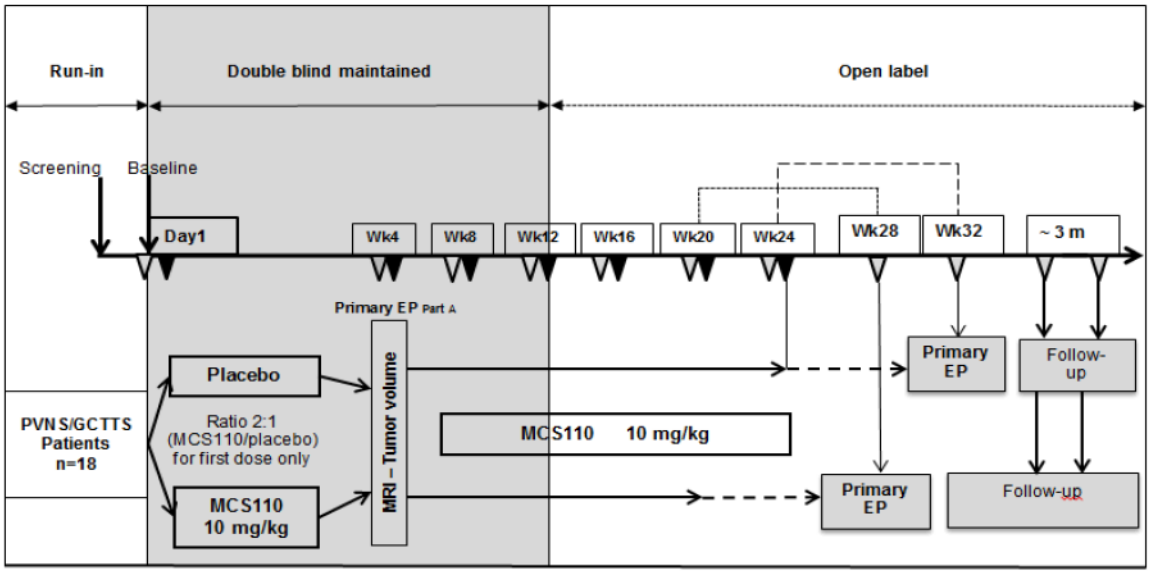
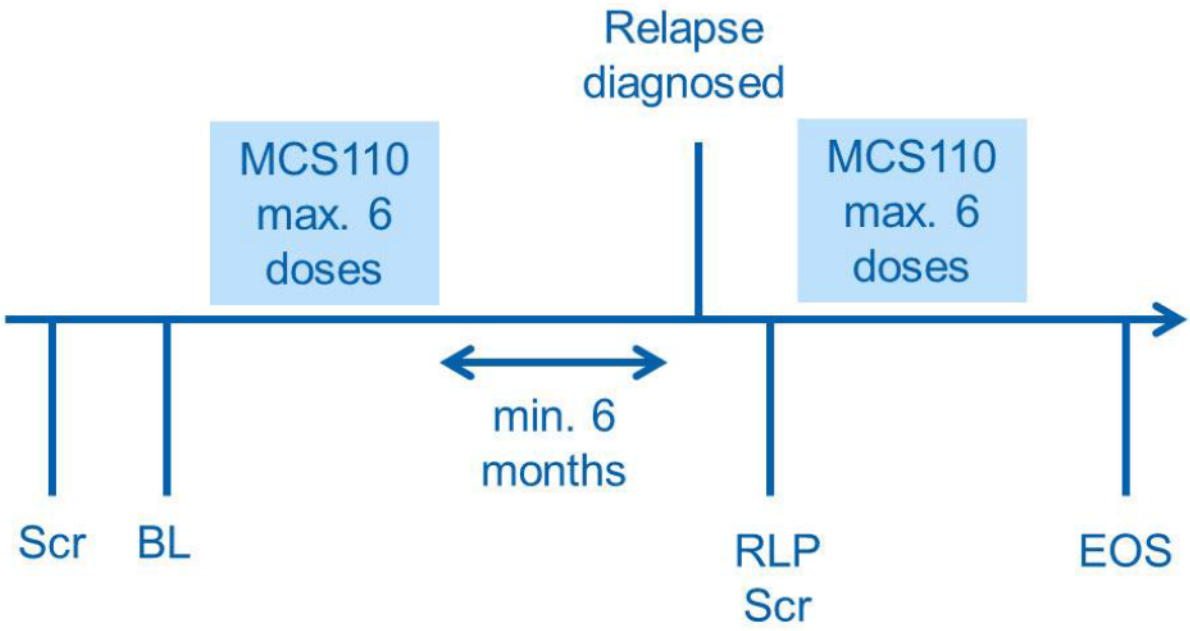


Figure 3-3 Study design re-dosing



3.2.2 Study design Part C

The study CMCS110X2201 Part C is a randomized, double-blind, parallel-arm adaptive dose exploration study part. Approximately 15 patients, including adults and adolescents (≥12 years old), will be randomized to receive 3 mg/kg, 5 mg/kg or 10 mg/kg MCS110 in a ratio of approximately 2:2:1 and a potential further extension of the efficient lower dose arm. Tumor volume reduction after 3 doses, assessed by MRI at week 12, will guide the decision on whether to continue with the initial dosing (3 mg/kg or 5mg/kg) or increase for the following three doses to 10 mg/kg to allow the patient to benefit from the drug.

The adult patients will follow Assessment schedule Part C.

The adolescent patients will follow Assessment Schedule Part C-Adolescent patients, adapted to reduce the required blood volume to maximum 25 mL per time point and 50 mL in 8 weeks (Howie 2011).

Conditions of dose level change after 3 doses

Patients enrolled in 3 mg/kg and 5 mg/kg arms: 3 additional MCS110 doses of the same dose will be administered, if MCS110 is well tolerated and if a reduction in tumor volume of ≥45% can be demonstrated after the 3rd MCS110 dose evaluated by MRI taken just before the 4th dose. This MRI is reflecting potential efficacy of 3 doses. If the drug is well tolerated and the tumor volume reduction is <45%, then three additional MCS110 doses of 10 mg/kg will be administered.

Process of dosing after 3 doses

All patients within each arm will receive 3 doses of the same initial dose at Day 1, week 4 and week 8.

At week 12, an MRI and safety examinations will be taken before the planned 4th dose. The unblinded statistician(s) and an unblinded Novartis medical person (unblinded safety reviewer) will review the tumor volume reduction data from baseline to week 12 MRI and patient's safety data. The unblinded safety reviewer will inform the site's unblinded pharmacist on the dose level to administer at week 12:

- Patients enrolled in 3 mg/kg and 5 mg/kg arms can receive same initial dose or increase to 10 mg/kg.
- Patients enrolled in 10 mg/kg arm: can either stop after 4 doses or receive up to 6 doses of 10 mg/kg under conditions described in the Section 5.5.5.2 (Dosing extension to 6 consecutive doses once every 4 weeks).

The primary outcome of Part C of the study will be the tumor volume after multiple doses of MCS110 determined by MRI which will be assessed 8 weeks after the last dose of MCS110.

Eligibility criteria and safety assessments will be similar as in Part B. Patients will also be followed up to 2 years Corporate Confidential Information or 1.5 years Corporate Confidential Information every 4 months and they will be offered another treatment course with 10 mg/kg of MCS110 in case of relapse, where relapse is diagnosed at least 6 months after the last MCS110 dose received during the first treatment course (Figure 3-3). Then, the adult and adolescent patients will follow Assessment Schedule Part C re-dosing.

Efficacy assessments will include tumor volume reduction,
, joint-specific questionnaires, VAS and time to relapse.

Conditions of lower dose arm recruitment extension

If a lower dose is identified with at least the same efficacy as 10 mg/kg, defined as tumor volume reduction evaluated by MRI of at least 45%, additional patients may be enrolled in this lower dose group to extend the arm up to approximately 10 patients. Only one dose level, either 3 or 5 mg/kg may be extended and the additional patients will be allocated to the selected dose level in an open label fashion with the same Assessment schedule Part C applied, Corporate Confidential Information

Figure 3-4 Study design Part C – adults and adolescent (Amendment 7)

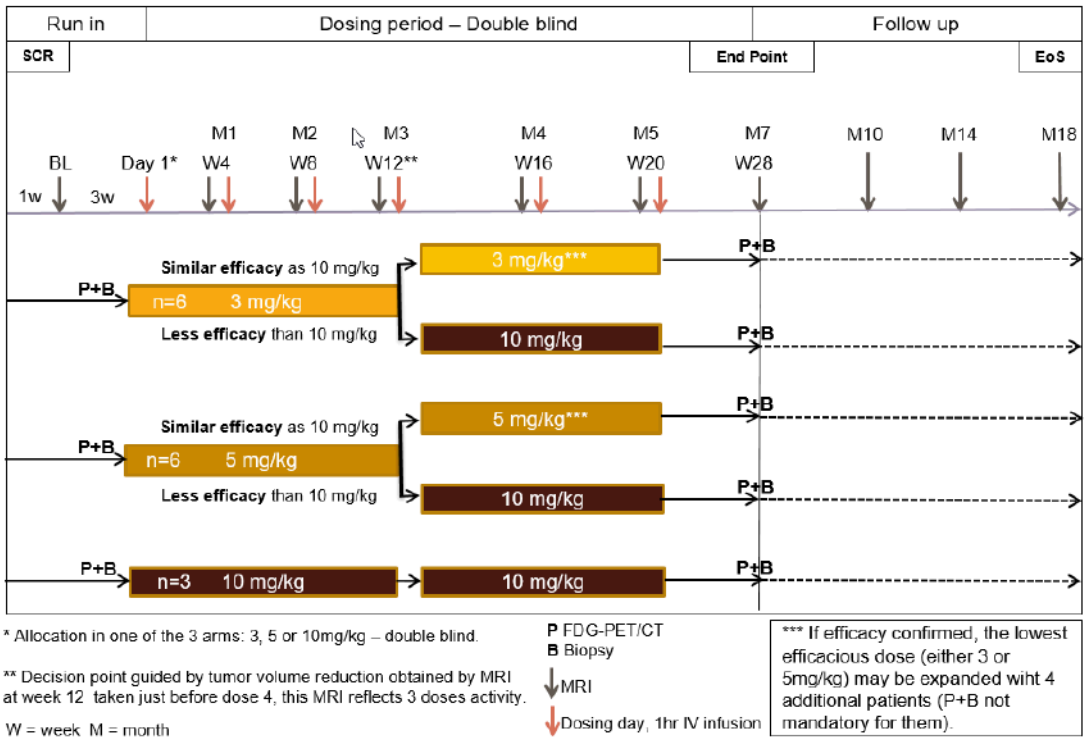
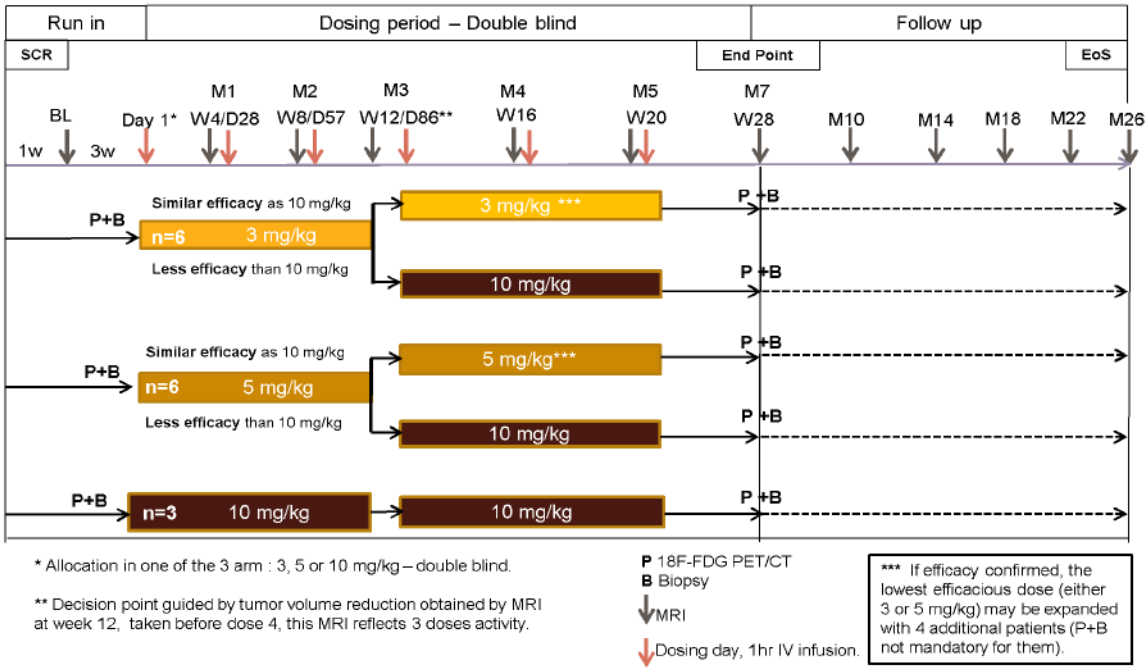


Figure 3-5 Study design Part C – adults and adolescents (Amendment 6)

As some patients will have followed study design of Amendment 6 we keep it in the protocol.



The planned enrollment number in Part C is approximately 15 patients. If a lower dose is identified to be, at least, as efficacious as 10 mg/kg, additional patients may be enrolled in open label to extend the efficacious 3 mg/kg or 5 mg/kg arm to approximately 10 patients.

3.2.3 Rationale for study design Part B and C

Study CMCS110X2201 is now designed as a three part study (amendment # 5). Part A is a single dose, placebo controlled, double-blind study in patients with PVNS. Due to the positive efficacy and safety data obtained in Part A it is now (amendment # 5) proposed to continue with a multiple dose open label study part to evaluate whether administration of multiple doses of MCS110 could result in complete tumor reduction. The primary endpoint for efficacy of multiple doses will be assessed 8 weeks post last dose. Frequent follow-up visits by patients every 3 months up to 2 years (in Part B and for protocol amendment 6 in Part C) or 1.5 years (after amendment 7) will allow early diagnosis and treatment of potentially recurring tumor.

3.2.3.1 Part B

The first dose of the multiple dose Part B will continue to be placebo controlled and double blind to complete the original study plan and analyze the reduction in tumor volume and symptoms after single dose and four weeks of treatment. Tumor growth is expected to be minimal within 4 weeks (<10%) and this has been confirmed so far in the one placebo treated patient with a tumor volume change of -2 %. As in Part A in Part B patients are randomized in a 2:1 ratio of active versus placebo to keep the number of placebo treated patients as low

as possible, but still allow assessment of active treated versus placebo treated patients. Patients will only receive a single dose of placebo and then will be shifted to active treatment. After the first dose, the multiple dose Part B will then continue as an open label study to allow all patients to benefit from 4 doses of MCS110 treatment. It is recognized, that subjective responses will be impacted by open label treatment, but 1) the primary outcome is longer-term tumor shrinkage, which is based on an objective measure and thus should not be affected by open label and 2) the study will have the first month's treatment blinded and the main clinical response seems to happen quite quickly (based on the first 5 patients), so this will still be an evaluable secondary endpoint at day 28.

Day 1 treatment will be maintained double-blind until week 12 when the fourth dose will be administered. Depending on the treatment received for the first dose, un-blinding will allow Day 1 placebo patients to receive 3 additional doses of MCS110 and Day 1 MCS110 patients to receive 2 additional doses of MCS110 up to a total of 6 consecutive dose administrations of MCS110.

3.2.3.2 Part C

Part C is a randomized, double-blind, parallel-arm adaptive dose exploration study. The goal of Part C is to identify a MCS110 dose lower than 10 mg/kg, which is as efficacious as 10 mg/kg, but may have less side effects. In order to proceed fast, two promising lower doses will be evaluated in parallel, 3 mg/kg and 5 mg/kg of MCS110. Simulations run using prior study information at week 12, log (ratio) of tumor size, and a conservative standard deviation estimate, show that 6 patients per arm in the 3 and 5 mg/kg groups will provide >80% power to declare the lower doses efficacious or not, compared to the 10 mg/kg group.

Once an efficacious lower dose will be identified either 3 mg/kg or 5 mg/kg, the identified arm may be expanded to up to approximately 10 patients for confirmation of safety and efficacy in more patients.

Rationale for assessment schedule C - Adolescent patients

The minimum body weight will be reduced to 30 kg, which is the lower range for children at the age of 12 years.

As per international guidelines for clinical trials in pediatric patients (Howie 2011), the blood volume collected at a time point from a subject 30kg body weight should must not exceed 25 mL per time point, and 50 mL in 8 weeks.

In order to comply with these recommendations only the key safety, PK, PD and Immunogenicity blood samples will be collected and analyzed (see Section 13 Appendix 1: Sample Log, Part C-Adolescent patients).

Risk assessment for effects of MCS110 on adolescent patients is described in the Section 3.5.2.

3.3 Rationale for dose/regimen, duration of treatment (Parts A and B and C)

For this first study in patients the dose of 10 mg/kg of MCS110 has been selected as the dose that had initially been identified as the highest tolerated single dose Corporate Confidential Information

In addition, a single dose of 10 mg/kg demonstrated pharmacodynamic effects suggesting target suppression up to 42 days, a 40% reduction in monocyte counts, and 80% reduction in bone resorption marker CTX-1 for at least 28 days.

MCS110 is administered by i.v. infusion, which is appropriate as the tumor is highly vascularized. By using the highest dose tolerated, we expect to maximize exposure of drug within the tumor, thus giving patients the best chance for a clinical benefit if there is one.
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Therefore, patients included in Part A of the proposed study are carefully monitored and appropriate dose adjustment to lower the dose is included in the protocol Corporate Confidential Information
In addition, all other potential adverse events will also be carefully monitored. There is no BMI limit for the patients to allow also obese patients to participate and potentially benefit from the study. As a monoclonal antibody, MCS110 is expected to largely distribute into blood and extra-cellular fluid spaces and then is expected to enter the highly vascularized tumor. In Part A no dose cap was applied in order to not under-dose patients with a body weight higher than 100 kg and maintain sufficient exposure at the target site for 28 days.

The follow-up period is planned to be 4 weeks, which is within the general time frame between diagnosis of PVNS and surgery. Corporate Confidential Information

3.3.1 Rationale for treatment with multiple doses (Part B and Part C)

In order to maximize the efficacious effect, the dose of 10 mg/kg MCS110 was maintained in the multiple dose Part B. For the multiple dose Part B initially a dosing regimen of 4 doses of 10 mg/kg MCS110 every 4 weeks was proposed. Corporate Confidential Information

Corporate Confidential Information Preliminary PK data have demonstrated comparable PK in patients with PVNS, which supports the application of this model to simulate multiple dosing regimen. Based on this, the readout for the primary end-point has been set at 8 weeks after the last dose, just before the exposure ends
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Following the primary outcome assessment at 8 weeks after the last dose of MCS110, Part B and C patients will be followed up every 3 months in Part B and every 4 months in Part C for up to approx. 2 years - or 1.5 years for amendment 7 - in order to monitor the duration of the tumor size response to MCS110. In case of relapse or regrowth of residual PVNS/GCTTS tumor during the follow-up period, a second treatment course can start if the patient tolerated MCS110 previously and had prior evidence of a clinically meaningful response (Figure 3-3).

In Part C it will be tested whether a lower dose (i.e. 3 mg/kg or 5 mg/kg) is as efficacious as 10 mg/kg MCS110 and whether the adverse event profile can be improved by lowering the dose.

Because the objective for Part C is to identify an optimal safe and efficacious dose rather than to characterize the full dose-response curve, both of these two promising lower doses will be tested in order to

maximize the potential for finding the optimal dose.

In Part Ca dose cap of a maximum dose of 1g MCS110 per infusion will be introduced (corresponding to a body weight of 100 kg for a dose of 10 mg/kg). At the preliminary analysis of the exposure and safety data, obese patient (n=1, wt = 140.2 kg, BMI 38.6) had highest exposure compared to rest of the patients. In that case, in order to avoid any potential over exposure associated AE, dose for patients over 100 kg will be limited to 1 g.

3.3.2 Rationale for treatment of adolescent patients (Part C)

PVNS has been reported to occur also in patients younger than 18 years old (Baroni et al 2010; Eckhardt and Hernandez 2004). A high medical need for treatment of PVNS and GCTTS in adolescent patients (12 to 17 years of age) has been identified by the study investigators. Those young patients with PVNS and GCTTS cannot undergo a surgery without worsening the function of their joint or they already have had multiple recurrences of the tumor. Medical treatment with MCS110 is expected to reduce the tumor volume and keep the disease under control or facilitate surgery or eliminate the tumor. Tumor tissue and vascularity is not considered to be different in adolescent patients compared to adult patients.

The exposure in patients with lower body weight has been modeled and is slightly lower with the same dose compared to a 70 kg patient, but this is not expected to have a pronounced effect on safety and efficacy: A simulation was run, considering the 1-hr iv infusion time of 10 mg/kg MCS110, every 4 weeks to patients with body weight of 20 kg (younger than 12 years old), 40 kg (12yrs old) and 70 kg (standard adult) (Figure 3-8). A standard allometric scaling of BWT^0.75 for clearance and BWT for volume of distribution are used, where BWT=body weight in Kg. The simulated typical concentration-time course shows at the same dose per body weight (here 10 mg/kg) that the exposure is slightly lower in children than in adults but would be largely overlapping with those in adults, when variability was taken into consideration.

From the safety point of view it is not likely to see more exposure related adverse events in children than in adults unless children are more sensitive to drug exposure, which is not expected.

Based on the known effects with antiresorptive agents on bone in children (Glorieux et al 1998; Land et al 2006), it is likely that MCS110 can be administered without serious consequences to an adolescent population for a limited period of time (6 months), and that the effects should be fully reversible after withdrawal of the compound.

From the efficacy point of view, if the exposure is at the plateau of exposure-response in adults, likely the dose would be efficacious enough in this group of children. That is, the difference in exposure might not be large enough to cause a difference in efficacy. This is consistent with most of the other drugs dosed in adolescent patients as compared to adult patients.

3.4 Rationale for choice of comparator

In Part A and first dose Part B, placebo is used as a comparator to obtain confirmation that during the natural course of the disease the tumor volume changes are very small in 4 weeks. It also allows to estimate or calculate the variability of the tumor volume analysis method by MRI, as this method has not been used or reported before for the quantitative measurement of PVNS tumors.

In Part B, the first dose will be compared to placebo (in a 2 MCS110:1placebo ratio) to continue to increase confidence in the original result from Part A, and to increase experience with change in PVNS tumor volume by MRI over a 4-week period. Repeat MRI measures of PVNS tumor volume have not been published in the literature. Patients who are assigned to placebo arm for the first dose in Part B will receive active drug MCS110 4 weeks later, then every 4 weeks up to a total of 6 doses.

Sufficient data on placebo were collected in Part A and B to get an estimation of the variability of the MRI assessment of tumor volume reduction. In Part C no placebo will be administered.

There will not be any active comparator, as there is no approved drug available today to treat PVNS.

3.5 Risk / Benefit for this study

Potential safety risks associated with MCS110 administration are based on data from Corporate Confidential Information patients with prostate cancer and bone metastasis, data collected in the single dose Part A and multiple dose Part B of this study, on non-clinical findings with MCS110, and on a recent report on another antibody to M-CSF, Pfizer's PD-0360.

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PVNS and GCTTS patients are generally, apart from their synovitis, healthy young to middle-aged adults. These diseases can occur also in children and adolescents and a high medical need for treatment of PVNS in adolescent patients (12-17 years of age) has been identified.

3.5.1 Possible MCS110-related risks

- Risks associated with MCS110 induced suppression of monocytes are infection or immunosuppression:

  A possible increased risk of infection due to a treatment induced reduction of monocytes is addressed by excluding individuals who have active infections or may have an increased risk of infection from intracellular organisms, particularly with pathogens cleared through the innate immune response. In Part A, since patients will undergo joint surgery as part of their routine care for PVNS, there is risks that post-operate infections will occur.

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  However, the decline in monocytes still leaves them within the normal range for adults; a literature search failed to find clinical conditions associated with monocytopenia and infections; Corporate Confidential Information

  In addition, patients will be closely monitored for clinical signs and symptoms of infection throughout the study. Complete blood counts (CBC's) with serum immunoglobulin profiles will be assessed regularly and collected at baseline, throughout the study and at the end-of-treatment. In addition, in the event that patients develop symptoms or signs of infection, all investigators and study sites will be instructed to perform evaluations appropriate for identification and treatment of the causative organism. At the time of the scheduled surgery in Part A, the PD effect of MCS110 on monocytes at 10 mg/kg is only expected to last approximately 10-14 more days, so if there is an immunosuppressive effect, it should be self-limited.

- Risks which are considered to be associated with MCS110 induced decrease in tissue macrophages: Kupffer cells, the macrophages in the liver, play an important role in the clearance of several serum enzymes, including AST/ALT and CK, which are typically elevated as a result of liver or skeletal muscle injury. Elevation of both enzymes has been observed in either pre-clinical and/or clinical studies after administration of M-CSF antibody and is considered to be the result of a reduction in Kupffer cells. In a recent paper, Pfizer investigators demonstrated that elevations of AST, ALT, and CK in monkeys and rats was related to Kupffer cell depletion and occurred in the absence of any hepatocellular or myocellular necrosis (Radi et al 2011).
  1. Hepatic effects: Corporate Confidential Information

     to minimize a possible liver effect, this trial will exclude individuals with a positive hepatitis serology or abnormal transaminase levels at screening and baseline.
  2. Muscle effects: In the recent report on an antibody to M-CSF administered to humans (Pfizer's® PD-0360324) (Sadis et al 2009), creatine kinase (CK) elevations up to 13.2x ULN were reported and one patient was reported to have asymptomatic, elevated CK and myoglobin levels, respectively. In study CMCS110X2101 with MCS110, dose limiting toxicity was identified at 20 mg/kg, based on elevation in serum creatine kinase (CK) exceeding 5 times the upper limit of normal in all subjects (3 out of 3). An upward trend in CK levels was observed also in the 10 mg/kg cohort with two subjects (out of 6 active) reaching 5 times upper limit of normal on Day 29. In the multiple dose part B, three subjects also showed transient CK increase >5 x ULN after one dose of 10 mg/kg MCS110. CK is an enzyme that denotes tissue insult or injury and is raised in acute liver damage but is also increased in response to muscle, kidney and brain tissue degradation. In CMCS110X2101 CK increase was always asymptomatic and without parallel elevation in troponin T (cTnT), indicative of heart tissue damage or aldolase, indicative of skeletal muscle damage. In addition, there were no symptoms of either skeletal or cardiac damage. As mentioned before, transient isolated CK elevation (with normal troponin T and aldolase) is considered due to a reduction in Kupffer cells, which are involved in the degradation of CK. In this study CK levels will be monitored closely and to assess a possible cardiac involvement of a CK elevation we will be measuring CK fractions (CK-MB) involvement, and troponin-T (cTnT). Macrophages play a significant role in muscle fiber membrane repair, regeneration and growth during increase muscle use after a period of atrophy (Tidball and Wehling-Henricks 2007). Therefore, patients must agree not to do heavy exercise (e.g., bodybuilding) throughout the study.

3. Effects on renal and lung macrophages: Monocyte derived cells are also found as mesangial cells of the kidney. Corporate Confidential Information patients with a history of renal diseases are excluded. Serum creatinine will be monitored to follow kidney function. Alveolar macrophages may be affected as well – although this was not observed in pre-clinical toxicology studies - and consequently patients with a history of lung disease are excluded from recruitment. Furthermore, monocyte derived cells are found as microglial cells in the brain as well as within the bone marrow, spleen, lymph nodes, skin and serosal surfaces. Patients will be closely monitored with physical examination to detect changes.

- Risks associated with MCS110 induced reduction in osteoclasts are hypocalcemia and hypophosphatemia and changes in bone turnover/homeostasis:
  Corporate Confidential Information

  Patients who are enrolled in this study must have normal serum ionized calcium and serum phosphate at screening and baseline and will be closely monitored for the calcium levels at regular intervals throughout the study. Patients who develop hypocalcemia or hypophosphatemia will receive immediate treatment and will be monitored at least on a weekly basis until they return to the normal range. Changes in bone turnover and bone homeostasis will be closely monitored. Corporate Confidential Information

- Risk of developing swelling: Corporate Confidential Information

  Two subjects in the highest dose group used in this study did develop non-pitting periorbital swelling; however, the overall conclusion of the abstract was that the therapy was tolerated well suggesting that Pfizer observed reversibility Periorbital swelling was observed in 1 of 5 patients in Part A, in 6 of 11 MCS110 treated patients in part B and in 15/18 patients in Part C. In all patients, periorbital swelling was mild and did not require any treatment. Periorbital swelling generally lasted between 6 and 30 days, however in one patient it was reported 2 times. The first time it lasted only a few days and the second time it lasted for almost 4 months. We will exclude patients with an increased risk in developing edema, such as those with renal, hepatic, or cardiac dysfunction. Furthermore, the development of swelling will be followed throughout the study by regular physical examination and serial body weight measurements.

- Risk of developing rash: With multiple dosing of MCS110 patients frequently developed rashes, 4/11 patients in Part B and 6/18 patients in Part C. Rashes, which occurred at both arms of upper extremity, on either hands or legs bilateral or neck, were generally reported as mild. Two adverse skin effects were reported as moderate, one patient who developed erythema nodosum and one patient who had eczematous dermatitis and pruritus.
- Risk of immunogenicity: Treatment with any exogenous protein therapeutic may cause immunogenicity with antibody formation against the drug. These antibodies may or may not be neutralizing, and may or may not affect the pharmacokinetics of the drug. When the drug is a naturally occurring protein, or closely related to one, then there is also risk of cross-reactivity to the native molecule, which may cause long-term adverse outcomes. However, when the molecule is a monoclonal antibody that inhibits a native protein target, as is the case for MCS110, then the risk of cross-reactivity is very low, and the main risk is loss of efficacy due to accelerated drug clearance (Krishna et al 2016). To date, we have not observed neutralizing antibodies to MCS110.

3.5.2 Possible study related risk

Risk of infusion reaction: In CMCS110A2101, of the 3 patients treated, one patient treated with MCS110 at the 0.01 mg/kg dose level experienced an infusion related reaction characterized by transient chills, hypotension, and dizziness 1 hour after completing the first MCS110 infusion with all 3 adverse events resolved approximately 1 hour after occurrence. The 2 other patients treated with MCS110 did not experience infusion reaction. Consequently, patients with a history of infusion reactions to, e.g., antibody treatment will be excluded. Corporate Confidential Information

In the ongoing part C (cut-off date: 19-Jan-2018) 5 patients experienced an infusion reaction, 4 of them during or directly after the first dose of MCS110. Two of the infusion reaction cases were classified as SAEs, but in both patients the infusion reactions resolved quickly after the administration of fluid and medications. Patients may receive pre-medication before the first infusion.

Risk from being exposed to radiation: This clinical study involves exposure to radiation Corporate Confidential Information (Part B: 3 times, optional; Part C: 2 times). Corporate Confidential Information

Risk from taking a biopsy by arthroscopy or via percutaneous needle: these methods are used in the diagnosis and treatment of disease or abnormalities of joints, including PVNS. It is possible, though unusual, to experience a bleeding episode during or after surgery or after a needle biopsy. This may require emergency treatment to drain accumulated blood. An infection risk is rare, but in case an infection occurs, treatment including antibiotics or additional surgery may be necessary. There may be temporary stiffness, swelling and pain after the procedure. There may be damage to the surrounding nerves or tendons. There may be the potential to develop an allergic reaction to tape, suture material, or topical preparations, which may require additional treatment.

Risk assesment for effects of MCS110 on bone parameters in skeletally mature patients with PVNS and their extrapolation to the immature skeleton:

Similar effects on bone biomarkers were described for two compound classes that target bone resorption, albeit by different mechanisms, namely the bisphosphonates (BPs) and the RANKL-inhibitor (Receptor Activator of NF-κB Ligand) denosumab (Prolia). Evidence obtained with antiresorptive treatments (BPs and RANKL-inhibitors) in children suggests that the suppression of osteoclast mediated bone resorption by 70% and more will lead to the appearance of radiographically visible transverse sclerotic bands (Glorieux et al 1998; Land et al 2006; Hoyer-Kuhn et al 2014). These bands may represent horizontal trabeculae formed during the temporary inhibition of epiphyseal activity (growth arrest lines) (Rauch et al 2014).

The width of the radiographically visible bands will depend on the duration of treatment and the growth velocity. Based on available evidence from the literature obtained with the RANKL inhibitor denosumab and various bisphosphonates, the effect should resolve after cessation of treatment (Wang et al 2014). The speed of this resolution will depend on two main factors: the thickness of the transverse sclerotic band and the degree of bone remodeling. Radiographic evidence disappears at approximately 4 years and 17 months after cessation of treatment for BPs and denosumab, respectively. This slow resolution is due to the long lasting antiresorptive effect of

BPs embedded on the bone surface, and the slow decrease of circulating antibody levels after stopping denosumab. Based on the difference in mechanism of action, it can be expected that the resolution of the bone effects will require less than 17 months when MCS110 treatment is stopped.

Taken together, based on the known effects of antiresorptive agents on bone in children, it is likely that MCS110 can be administered without serious consequences to an adolescentpopulation for a limited amount of time such as 6 months, and that the effects should be fully reversible after withdrawal of the compound.

3.5.4 Placebo treatment

3.5.4.1 Part A

Placebo treated patients will not experience an immediate benefit by participating in this study. The risks associated are basically related to the infusion as discussed above. The minimum of 4 weeks treatment period in between diagnosis of PVNS and surgery is within the normal time period and untreated tumor growth is considered minimal. The time to diagnosis of PVNS can be 2-3 years.

3.5.4.2 Part B

First dose placebo treated patients will not experience an immediate benefit by participating in this study. After the first dose, patients will receive MCS110 4 weeks later. The risks associated with the placebo infusion are basically related to the infusion as discussed above.

3.5.4.3 Part C

Placebo treatment will not be used in Part C.

3.5.5 Risk/benefit assessment

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Any potential immunosuppressive risks of MCS110 should be self-limited after the dose is cleared. Potential development of periorbital edema and rash, which was observed frequently with multiple doses of 10 mg/kg MCS110 is expected to be mild and reversible and not expected to occur with the lower doses tested. Patients will only be re-dosed once the AE resolved. If lower dose is not efficacious, patients will receive 3 doses of 10 mg/kg MCS110 to allow for tumor volume reduction. Based on the known effects of antiresorptive agents on bone in children, it is likely that MCS110 can be administered without serious consequences to an adolescent population for a limited amount of time such as 6 months, and that the effects should be fully reversible after withdrawal of the compound.

Adherence to the inclusion and exclusion criteria and close clinical monitoring are considered sufficient to minimize the potential risks to the patients.

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4 Population

The study population will be comprised of males and females aged 18 (in Part C ≥12) or older and diagnosed with PVNS (Part A) or GCTTS (giant cell tumor of the tendon sheath). Up to 18 evaluable patients were recruited in total in Parts A and B and approximately 19 patients will be recruited in Part C (approx. 15 in double blind phase and if a new efficacious dose is determined, 4 additional patients will be recruited in this arm in open label), where "evaluable" patient is defined as completing the protocol through follow-up MRI (approximately day 28 for Part A and earliest after second dose for Part B and after the third dose for Part C); patients who are dosed but are not evaluable will be replaced at the discretion of the sponsor. Part A recruitment will continue until amended protocol Part B is approved by IRB. Part B patients will continue in follow-up in parallel of Part C patients. The investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional exclusions should be applied by the investigator, in order that the study population will be representative of all eligible patients.

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

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

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

4.1.1 Part A

1. Men and women aged ≥ 18 years with diagnosis of PVNS, who have at least one measurable site of disease on MRI and are expected to undergo surgery, will be eligible to participate in the study. The diagnosis of PVNS should be based on clinical assessment and MRI, with or without biopsy confirmation.

4.1.2 Part B

1. Men and women aged ≥ 18 years with diagnosis of PVNS or GCTTS, who have at least one measurable site of disease on MRI will be eligible to participate in the study. The diagnosis of PVNS or GCTTS should be based on clinical assessment and MRI, with or without biopsy confirmation.

4.1.3 Part C

1. Males and females aged ≥ 12 years with diagnosis of PVNS or GCTTS, who have at least one measurable site of disease on MRI will be eligible to participate in the study. The diagnosis of PVNS or GCTTS should be based on clinical assessment and MRI, with or without biopsy confirmation.

Adolescents (≥ 12, <18 years old) eligible for enrollment need to have (1) symptomatic disease for which surgical intervention is indicated and the surgical procedure itself would be associated with significant morbidity or (2) recurrent disease.

4.1.4 Parts A, Part B and Part C

1. Written informed consent must be obtained before any assessment is performed.
   For adolescent patients, written informed consent is required from the legal representative and the adolescent must assent to participation.
2. At Screening, and Baseline, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the patient has rested for at least three (3) minutes. Vital signs should be within the following ranges:
   - oral body temperature between 35.0-37.5°C
   - systolic blood pressure, 80-150 mm Hg
   - diastolic blood pressure, 50-100 mm Hg
   - pulse rate, 40 - 100 bpm.

   If vital signs are out-of-range, the Investigator may obtain two additional readings**,** so that a total of up to three (3) consecutive assessments are made, each after at least 5 minutes and with the patient seated quietly during the five (5) minutes preceding the assessment. All blood pressure measurements at other time-points should be assessed with the patient seated, and utilizing the same arm for each determination. ***At least the last reading must be within the ranges provided above in order for the patient to qualify.***
3. Patients must have serum ionized calcium and phosphate (PO_4) levels within normal range.
4. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 84 days (time for > 99.9% of the study drug to be cleared from the circulation) after the last study drug infusion. **Highly effective contraception methods include**:
   - Total abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - Male partner sterilization (at least 6 months prior to screening,). For female study patients, the vasectomised male partner should be sole partner for that patient.
   - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

   In case of use of oral contraception women should be stable on the same contraceptive medication for a minimum of 3 months before taking study treatment.

   Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical

profile (i.e., age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

A pregnancy test will be done on all female patients regardless of reported reproductive status at specified time points throughout the study.

5. Sexually active males must use a condom during intercourse while taking drug and for 84 days after stopping investigational medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
6. Patients must weigh at least 30 kg (Part A and B: at least 40 kg) to participate in the study, and be able to fit in the site's MRI machine. If the weight exceeds 100 kg, a dose will be capped at 100 kg (max. 1g of MCS110 per infusion).
7. Patients must be able to communicate well with the investigator, to understand and comply with the requirements of the study, and to understand and sign the written informed consent.

4.2 Exclusion criteria

4.2.1 Parts A, Part B and Part C

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study:

4.2.2 Part A

1. Patients with PVNS, who have had more than two operations on the affected joint (not including diagnostic biopsies) or have received chemotherapy or radiation therapy to treat PVNS. Previous operations to a different joint from the one now being treated are not exclusionary.

4.2.3 Part B and Part C

1. Patients with PVNS or GCTTS whose tumor is not evaluable by MRI, in the judgment of the central MRI reading site.

4.2.4 Parts A, Part B and Part C

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study:

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations.
2. A known hypersensitivity to the study drug or drugs similar to the study drug. Patients who ever experienced a cytokine release syndrome/acute infusion reaction in response to treatment with an agent (e.g., monoclonal antibodies or other biological agents) are also excluded.
3. Patients who have undergone major surgery $\leq$ three (3) months prior to starting study drug or who have not recovered from side effects of such therapy.

4. Patients with a history of coagulation disorders (hemorrhage or thrombosis).
5. Any systemic illness that increases the risk to patients due to potential immunosuppression:
   a. Congestive heart failure, cancer (with the exception of excised superficial lesions such as basal cell carcinoma and squamous cell carcinoma of the skin), uncontrolled diabetes mellitus (fasted glucose > 180 mg/dL,), rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, or other chronic inflammatory disease.
   b. History or serological evidence of HIV infection, hepatitis B or C infection (positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result in adults).
   c. History or serological evidence of active or latent tuberculosis (TB) as indicated by a positive QuantiFERON (in adults) or PPD skin test (in adolescents) at screening.
   d. History of systemic fungal infection (e.g., histoplasmosis, coccidiomycosis, etc.) or systemic bacterial infection requiring parenteral antibiotic therapy within the past two years.
   e. Evidence of any unresolved infectious illness within the past 2 weeks.
6. Pregnant or nursing (lactating) women.
7. Use of any intraarticularly administered drug (to the joint affected by PVNS) within 4 weeks prior to dosing.
8. For patients ≥18 years old: Donation or loss of 400 mL or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation. For patients ≥12 - <18 years old: loss of ≥ 10% of blood within eight (8) weeks prior to screening, or longer if required by local regulation. The total blood volume of a child should be calculated based on the WHO recommendation (Howie 2011).
9. Hemoglobin level below 11.5 g/dL at screening.
10. Recent (within the last three [3] years) and/or recurrent history of acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated), or history of atopic allergy (asthma, urticaria, eczematous dermatitis).
11. Evidence of liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), γ-GT, alkaline phosphatase, or serum bilirubin.
    a. Any ***single parameter*** may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more ***as soon as possible***, and in all cases, at least prior to enrollment/randomization, to rule out lab error.
    b. Any elevation of more than one parameter excludes a patient from participation in the study. Testing may be repeated once more as soon as possible, but in all cases, at least prior to enrollment/randomization, to rule out lab error.

       Re-check results must be within normal limits in order for patient to qualify.
12. History or presence of impaired renal function as indicated by clinically significantly abnormal creatinine or BUN and/or urea values, or abnormal urinary constituents (e.g., albuminuria).
13. Patients with elevated troponin T and/or CK levels (> 1.5 x ULN for the laboratory) or with history of myositis, rhabdomyolysis or other myopathic disease.

14. Concomitant disease(s) known to influence calcium metabolism of bone, including hyperparathyroidism, hyperthyroidism, Paget's disease, osteogenesis imperfecta, and/or osteomalacia.
15. Patients with dermal change indicative of lymphedema, or phlebolymphedema; specifically, any trace thickening, faint discoloration, swelling or obscuration of anatomic architecture on close inspection suggesting edema and no pitting edema at any site, particularly head (periorbital), neck, trunk, genital and visceral areas.
16. Patients who are currently receiving immunosuppressive treatment, including systemic corticosteroids greater than the equivalent of 10 mg of prednisone, which cannot be discontinued at least 4 weeks prior to starting study drug.
17. Farm workers or patients who drink un-pasteurized milk.
18. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening and baseline.
19. Active or latent tuberculosis (TB as indicated by a positive QuantiFERON or PPD skin test at screening).
20. Patients engaged in or planning to enter a resistance exercise training program. Occasional training (≤ once per week) or previously routine low-impact aerobic exercise (running, bicycling, etc.) is permissible. Patients must not commence any such activities until the end of the study, except under the treatment of a post-operative rehabilitation program as prescribed by their clinician.
21. Patients with pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin or body and patients who are unable to undergo MRI due to claustrophobia will be excluded.
22. Patients who are unable to undergo MRI will be excluded.

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

5 Treatment

5.1 Investigational treatment

The investigational drug, MCS110, will be prepared by Novartis and supplied to the Investigator as open labeled bulk medication.

- Name: MCS110
- Formulation: Liquid in Vial (Concentrate for solution for infusion)
- Unit dose: MCS110 150MG Liquid in vial 7.5ML

5.1.1 Bio-batch Retention samples

Not applicable.

5.2 Treatment arms

5.2.1 Part A

Patients will be assigned to one of the following 2 treatment arms in a ratio of 2:1 MCS110 to placebo.

5.2.2 Part B

For the first dose, patients will be assigned to one of the following 2 treatment arms in a ratio of 2:1 MCS110 to placebo. All patients from the second and subsequent doses will receive MCS110 in open label.

5.2.3 Part C

Approx. 15 patients (including adults and adolescents ≥12 - <18 years old) will be randomized in double-blind manner to one of the following 3 parallel arms: 3 mg/kg or 5 mg/kg or 10 mg/kg of MCS110 in a ratio of approximately 2:2:1.

In case a lower dose is identified to be at least as efficacious as 10 mg/kg after 3 doses, additional 4 patients may be enrolled in this lower dose group and randomized in an open label fashion to a total of approximately 10 patients.

Table 5-1 Treatment arms in Part C

Treatment	Double-blind	Potential open label extension
3 mg/kg	n ~6	n ~4*
5 mg/kg	n ~6	n ~4*
10 mg/kg	n ~ 3	n=0

*Either 3 or 5 mg/kg may be expanded.

5.3 Treatment assignment

Treatment / randomization numbers will be assigned in ascending, sequential order to eligible patients in accordance with entry into the study. The treatment / randomization number becomes the definitive patient number as soon as a patient receives the first dose of the respective study treatment.

The investigator will enter the randomization number on the CRF (eCRF). The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for patients will be reviewed and approved by a member of the Biostatistics Quality Assurance Group.

When an eligible patient at a study site requires randomization into the study, the study nurse or the unblinded pharmacist/designee at the study site will complete an application to the assigned randomization coordinator who will then issue a randomization number. The unblinded pharmacist/designee will then ensure that the correct study medication is prepared, according to the corresponding Treatment Allocation Card of the assigned randomization number. Full details of this process are documented in the Randomization Manual.

5.4 Treatment blinding

Part A and first dose Part B

This is a double blind study: patients, investigator staff (except the unblinded pharmacist), persons performing the assessments, and data analysts will remain blind to the identity of study treatments according to the specifications provided in Appendix 2.

A safety review will be carried out after each patient completes the 4-week treatment period, therefore the independent safety reviewer will be unblinded on an ongoing basis.

Randomization data are kept strictly confidential until the time of unblinding for the respective person(s). Further information regarding blinding and unblinding is presented in Appendix 2. The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration and appearance. Unblinding will only occur in the case of patient emergencies (see Section 5.5.10), at the time of the interim analysis and at the conclusion of the study.

Part B

Double-blind study part will be followed by an open label part from the second to the sixth dose.

Day 1 treatment will be maintained double blinded until week 12. At week 12, Day 1 treatment will be un-blinded in order to allow Day 1 placebo patients to receive two more MCS110 doses in open label.

Part C

28 weeks double-blind treatment period study part will be followed by an open label part.

Day 1 treatment will be maintained double-blinded until primary endpoint reached at Week 28 (or until any premature primary endpoint) to the Novartis clinical team and the investigator.

Following week 12 MRI, Novartis independent statistician (independent from the clinical study team) will proceed to the un-blinding and will share allocated dose level with an unblinded Novartis medical person (independent from the clinical team) who will review patient's safety profile and tumor volume reduction. The unblinded medical person will determine if the patient fulfills dose change conditions. The site's unblinded pharmacist will be informed by an independent study team member of potential dose change.

5.5 Treating the patient

5.5.1 Patient numbering

Screening number

Each patient screened is assigned a unique screening number. The screening number is a combination of the center number that is provided by Novartis, and a four digit number starting with 0001 for each patient which is assigned by the Investigator. Therefore, if the center number is 3001 (any leading 0's in the center number are dropped) the screening numbers will be assigned such as 3001_0001, 3001_0002, 3001_0003 in ascending order. If the center number is 3002, the screening numbers will be 3002_0001, 3002_0002, 3002_0003 in an ascending order.

Randomization / treatment number

If the patient is deemed eligible for enrollment into the study and will commence dosing, a randomization/ treatment number will be assigned. Once assigned to a patient, a treatment number or randomization number will not be reused.

There should be a source document maintained at the site which links the screening number to the randomization / treatment assignment number (once assigned). Patients will be assigned treatment numbers, 5101-5118. Replacement patients will be assigned treatment numbers, 6101-6118. If a patient requires a replacement, the replacement patient will be assigned a treatment number corresponding to the original patient (e.g., Patient 6103 would replace Patient 5103).

In Part C, patients will be assigned treatment numbers, 5119-5148, and potentially 5150– 5158, if arm extension is done for the efficacious lower dose. Replacement patients will be assigned treatment numbers, 6119-6148; 6150-6158. If a patient requires a replacement, the replacement patient will be assigned a treatment number corresponding to the original patient (e.g., Patient 6120 would replace Patient 5120). The randomization numbers 5149 and 6149 are not going to be used in the study Part C.

The Table 5-2 details the general details of the numbering of the patients once assigned / randomized to treatment:

Table 5-2 Treatment Assignment Numbering

Arm	Randomization numbers	Replacement randomization numbers
I (n=18)	5101 – 5118	6101 – 6118
II (n=30)	5119 - 5148	6119 - 6148
III (n=8: potential extended arm)	5150 – 5158	6150 - 6158

5.5.2 Dispensing the study treatment

For preparation of the study medication, a copy of the treatment allocation cards will be sent to the pharmacist / technician at the Investigator's site.

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

Bulk medication labels will be in the local language, will comply with the legal requirements of each country, and will include storage conditions for the drug but no information about the patient.

5.5.3 Supply, storage and tracking of study treatment

Study drugs must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access. Upon receipt, the study drugs should be stored according to the instructions specified on the drug labels.

Storage conditions must be adequately monitored and appropriate temperature/humidity logs maintained as Source data.

The Investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be verified by the Monitor during site visits and/or at the completion of the trial.

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

At the conclusion of the study, and, if allowed during the course of the study (e.g., an open label study or an un-blinded monitor), the Investigator will provide a copy of the drug accountability ledger to the Monitor.

Only after receiving a written authorization by Novartis, the Investigator/designee will send all the unused and partly used drug supplies as well as the empty containers to the address provided at the time of authorization for destruction or have the unused and partly used drug supplies as well as the empty containers destroyed by the site's pharmacist, providing a drug destruction certificate.

5.5.4 Instructions for prescribing and taking study treatment

Part A and first dose Part B

A single dose of MCS110 at 10 mg/kg will be administered on day 1. Patient dosing should occur within 7 days after validated reference MRI was performed.

Part B from dose 2 to dose 6:

A single dose of MCS110 at 10 mg/kg will be administered on weeks 4, 8, 12, 16, and 20. Patient dosing should occur after follow-up MRI was performed.

Part C from dose 1 to 6:

A single dose of treatment (3, 5 or 10 mg/kg) will be administered on Day 1 and weeks 4, 8, 12, 16, and 20. Patient dosing should occur after follow-up MRI was performed.

Part A, Part B and Part C

Administration will be by regular infusion (gravity or pump assisted). The intravenous infusion will last for 1 hour ±10 minutes. The dose will be calculated from the individual patients' body weight as measured at the baseline visit and subsequent visits prior to the administration. The infusion duration is based on safety consideration, as it allows termination of infusion in case immediate adverse events arise.

The patient should be monitored in the clinic for 4 hours from the end of dosing. The study medication preparation guidelines are described in the Dose Preparation and Administration Manual.

During the MCS110 infusion, the patient's vital signs (blood pressure, pulse, respiration and temperature) will be monitored every 15 ± 5 minutes for the duration of the infusion and at the time of discontinuation of the infusion. In addition, vital signs will be monitored post infusion.

The infusion should be slowed or stopped and the responsible physician notified immediately should any of the following conditions apply:

1. Systolic blood pressure is more than 20 mm Hg above or below baseline (Note: If blood pressure drops ≥ 30 mm Hg, the infusion should be stopped immediately).
2. Pulse is more than 20 beats per minute above or below baseline or if pulse is irregular.
3. Temperature is > 38.5°C.
4. There are other clinical signs or symptoms of a hypersensitivity or infusion reaction (e.g., rigors, dyspnea, hypoxia and wheezing).

In addition, the drug infusion may be stopped at any time at the discretion of the investigator for an adverse event of lesser severity.

In case of an infusion reaction appropriate treatment should be administered as described in Table 5-3 and in Table 5-4. If infusion reactions symptoms have improved after interruption, the infusion can be resumed at one-half of the previous rate. The rate of infusion can only be reduced twice.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF (eCRF).

5.5.5 Permitted dose adjustments and interruptions of study treatment

5.5.5.1 Part A

If CK > 5 x ULN occurs in 2 patients, subsequent patients may be treated with a lower dose. Such a change will be implemented via an amendment to the protocol.

In the event of a severe infusion reaction, the investigator should stop the infusion of MCS110 immediately and the patient must be discontinued from the study (Table 5-3).

Table 5-3 Criteria for addressing infusion/hypersensitivity reactions in Part A

Allergy/Immunology	Action
Infusion-related reaction / hypersensitivity	Maintain dose level.
Flushing; rash; urticaria; dyspnea; drug fever ≥38.5°C/≥101.3°F or symptomatic bronchospasm, with or without urticaria[a]; allergy-related edema/angioedema; hypotension (characterized by a systolic pressure drop ≥ 30 mm Hg) or anaphylaxis [b]	Immediately stop MCS110 infusion and discontinue patient from study. Medication such as anti-histamines or corticosteroids should be given for symptomatic relief. Epinephrine can be indicated when wheezing and anaphylaxis of acute life-threatening nature is present but should be chosen cautiously.

[a] Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity.

[b] Anaphylaxis is defined as vascular collapse and shock (blood pressure < 90 mm Hg that is unresponsive to IV fluids) believed to be allergic in origin, with or without antecedent respiratory distress and occurring within 30 minutes of initiation of MCS110 infusion. Cutaneous manifestations include pruritus, urticaria, or angioedema.

5.5.5.2 Part B and Part C

Dosing adjustment due to safety issues / adverse events

In the event of a severe infusion reaction, the investigator should stop the infusion of MCS110 immediately and the patient must be discontinued from the study (Table 5-2).

Patients may receive pre-medication before the first infusion [anti-histamine (diphenhydramine 50 mg or equivalent) and acetaminophen (1 g)].

Table 5-4 Criteria for addressing infusion/hypersensitivity reactions in Part B/C

Toxicity CTCAE grade (value)	Action
Infusion-related reaction/ hypersensitivity	
Grade 1: transient flushing or rash, drug fever <38°C/ < 100.4°F	Maintain dose level. May premedicate at subsequent infusions with anti-histamine (diphenhydramine 50 mg or equivalent) and acetaminophen (1 g). Patients must then be observed for at least 3 hours after each subsequent infusion before being discharged from the treatment center.
Grade 2: flushing, rash, urticarial, dyspnea, drug fever ≥38.5°C/≥101.3°F	Interrupt the infusion of MCS110, administer anti-histamines or corticosteroids to be given for symptomatic relief. After recovery of symptoms, resume the infusion at a slower rate (50% of previous rate) and, if no further symptoms appear, complete the administration of the dose.
Toxicity CTCAE grade (value)	Action
Grade 3: symptomatic bronchospasm, with or without urticaria[a]; allergy-related edema/angioedema; hypotension (characterized by a systolic pressure drop ≥ 30 mm Hg)	Immediately stop MCS110 infusion and discontinue patient from study. Medication such as anti-histamines or corticosteroids should be given for symptomatic relief.
Grade 4: anaphylaxis[b]	Immediately stop MCS110 infusion and discontinue patient from study. Epinephrine can be indicated when wheezing and anaphylaxis of acute life-threatening nature is present but should be chosen cautiously.

[a] Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity.

[b] Anaphylaxis is defined as vascular collapse and shock (blood pressure < 90 mm Hg that is unresponsive to IV fluids) believed to be allergic in origin, with or without antecedent respiratory distress and occurring within 30 minutes of initiation of MCS110 infusion. Cutaneous manifestations include pruritus, urticaria, or angioedema.

If a patient develops periorbitalswelling, subsequent dosing (e.g., 4 wks, 8 wks) will be put on hold until one week after the swelling has resolved.

If a patient develops any adverse event considered as drug related by the investigator, which has not resolved before the following dose, next dosing will be delayed until considered resolved.

If there are abnormal hematology and / or biochemistry laboratory values (CTCAE grade 3) judged as clinically significant by the Investigator, the next dose will be delayed until abnormalities have resolved. Isolated CK increase with normal troponin T and aldolase is not considered a safety concern even if reaching CTCAE grade 3.

Part B: If dosing of 4 times 10 mg/kg MCS110 (once every 4 weeks) is exceeding the initial 13 weeks dosing period, (due to occurrence of AEs) further dosing will be allowed up to week 20 if all AEs had resolved for more than a week and efficacy assessment demonstrates response to treatment (>50 % of tumor volume reduction after 3rd dose in Part B, 45% in Part C) of these patients.

Dosing extension to 6 consecutive doses once every 4 weeks

Patients initially receive 4 consecutive doses once every 4 weeks (week 0, 4, 8, 12). Patients will receive 1 or 2 additional doses under the following conditions:

- no treatment related safety issues (for periorbital swelling* only if >grade 2) resulting in dosing delay during the first 4 doses the tumor has not been completely eliminated after the 3rd dose [determined by MRI at week 12]
- the tumor did respond to treatment (Part B: >50 % tumor volume reduction) after the 3rd dose [determined by MRI at week 12]

In Part C additional criteria apply as following:

- Part C (arms 3 mg/kg or 5 mg/kg): the tumor did respond to treatment (≥45 % tumor volume reduction) after the 3rd dose [determined by MRI at week 12] and MCS110 was tolerated: the patient will receive 3 additional doses of the same as dose level
- Part C (arms 3 mg/kg or 5 mg/kg): the tumor response to treatment is <45 % of tumor volume reduction after the 3rd dose [determined by MRI at week 12] and MCS110 was tolerated: the patient will receive doses increased to 10 mg/kg
- Part C (arm 10 mg/kg): the tumor did respond to treatment (≥45 % tumor volume reduction) after the 3rd dose [determined by MRI at week 12] and MCS110 was tolerated: the patient will receive 3 additional doses of 10 mg/kg
- Part C (arm 10mg/kg): the tumor response to treatment is <45 % of tumor volume reduction after the 3rd dose [determined by MRI at week 12] and MCS110 was tolerated: the patient can receive 1 additional dose of 10 mg/kg

New treatment course in case of recurrence of tumor or regrowth of residual tissue

If, based on MRI, relapse is identified, it is possible to start an additional course of 6 consecutive doses of MCS110 10 mg/kg, if there was:

- Good tolerability of MCS110 during the first treatment cycle
  - Patient received 6 doses
  - No early treatment discontinuation

- Good response in tumor volume reduction:
  Tumor volume reduction at (up to) 1°EP (8 wks post last dose of 6 doses) of >50% during the 1st treatment cycle
- Relapse defined as:
  - Symptoms (pain, swelling, redness, stiffness) and
  - Tumor volume increase greater than 50% of the difference between tumor volume at BL and the lowest tumor volume measured by MRI.
- Last dose of MCS110 was at least ≥ 6 months ago.
- Inclusion/exclusion criteria are still fulfilled.

During the second treatment course safety monitoring will be the same as during the first treatment course. Efficacy will be assessed by MRI after the 3rd dose at week 12 to decide on dosing beyond 4 doses and then again 8 weeks post last dose. Once a lower dose with same efficacy as 10 mg/kg has been identified in Part C, relapse patients will receive the lower dose treatment. During the second treatment course no placebo dose will be administered.

5.5.6 Rescue medication

Not applicable.

5.5.7 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug eCRF.

All prescription medications and over-the-counter drugs taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant Medications/ Non-Drug Therapies page of the eCRF.

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

Allowed medication

- Adjuvant radiation therapy as clinical standard of care after surgery (only for Part A).
- Patients on treatment with cholesterol lowering medication or anti-hypertensives can continue with their medication, but it must be documented in the Concomitant medications / Significant non-drug therapies page of the eCRF.
- Diabetes drugs (in Part C)
- If needed, paracetamol / acetaminophen and NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are acceptable, but must be documented in the Concomitant medications / Significant non-drug therapies page of the eCRF. NSAIDs must be discontinued prior to surgery according to local practice. All pain medication must be discontinued 24h prior to QoL questionnaires assessments at time-points according to Assessment Schedule.

- Patients may receive pre-medication before the first infusion [anti histamine (diphenhydramine 50 mg or equivalent) and acetaminophen (1 g)] or patients with mild infusion reactions, may premedicate at subsequent infusions with anti-histamine (diphenhydramine 50 mg or equivalent) and acetaminophen (1 g). Patients must then be observed for at least 3 hours after each subsequent infusion before being discharged from the treatment center.

5.5.8 Prohibited treatment

Parts A and B:

Diabetes drugs, cancer drugs, immunosuppressants and biologics are not allowed.

Part C:

Cancer drugs, immunosuppressants and biologics are not allowed.

Parts B and C:

Tumor aspiration is not allowed during the treatment phase (can be performed only after 8 weeks follow-up MRI of last dose).

5.5.9 Discontinuation of study treatment and premature patient withdrawal

Study "Stopping rules"

The study will be put on hold and no further dosing will be taken pending a full safety review, if any of the following criteria are met:

1. 1 or more study-drug related SAEs are reported.
2. At least 2 patients in the active arm experience a similar AE which is assessed as either moderate or severe in intensity, and is potentially related to study-drug. Periorbital edema that resolves will not lead to study cessation, as noted above.
3. Only Part A: CK > 5 x ULN (CTCAE grade 3) (CTCAE, version 4.0) occurs in 2 patients on active treatment.

Individual patient withdrawal

Part A

As this is a single dose study, treatment interruption will occur only if there is evidence of an infusion reaction during study drug administration (Table 5-3).

Parts A, Part B and Part C

Patients or legal representatives may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a

patient's premature withdrawal from the study and record this information on the Study Completion eCRF.

Part B and Part C

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

Treatment interruption will occur if there is evidence of an infusion reaction during study drug administration (Table 5-4) or any other adverse event which in the opinion of the investigator warrants discontinuation of the infusion.

Discontinuation of study treatment and patient withdrawal will be at the discretion of the Investigator, under the following circumstances:

- Infusion-related adverse event, such as hypotension, rash, or other evidence of an infusion reaction while the infusion is still running.
- Any other protocol deviation that results in a significant risk to the patient's safety.

Study treatment must be discontinued and the patient withdrawn from the study if one the following occurs:

- Patient or the legal representative withdraws consent
- Pregnancy
- Severe hypersensitivity reaction
- Drug-related SAE

Patients who discontinue prematurely the study treatment will proceed directly to the follow-up phase (the remaining dosing visits for these patients will be omitted).

All patients receiving MCS110 who experience a severe AE or SAE must have follow-up evaluations until resolution or stabilization of the symptoms. For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Part A

Patients who are prematurely withdrawn from the study (before day 29) for reasons other than safety will be replaced by an equal number of newly enrolled patients.

Part B

Patients who are prematurely withdrawn from the study before to receive 2 doses of MCS110 and perform follow-up MRI for reasons other than safety will be replaced by an equal number of newly enrolled patients.

Part C

Patients who are prematurely withdrawn from the study before to receive 3 doses of MCS110 and perform follow-up MRI for reasons other than safety will be replaced by an equal number of newly enrolled patients.

5.5.10 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. A complete set of emergency code break cards will be provided to the investigator site(s) and a complete set will be available at Novartis. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible in case of emergency. The investigator will receive a blinded code break card for each patient, with the details of drug treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. **The unblinded treatment code should not be recorded on the eCRF.** The investigator must also immediately inform the Novartis local monitor that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the code break cards in case of emergency. If appropriate, the investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable.

5.5.11 Study completion and post-study treatment

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

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.12 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 6 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6 Visit schedule and assessments

The full Part A, Part B and Part C Assessment Schedules are presented before Section 1.

Assessment Schedule Part B after week 12, presents 2 parts to apply:

- If patient received Day 1 placebo, Assessment Schedule Part B1 applied after Visit 7
- If patient received Day 1 MCS110, Assessment Schedule Part B2 after Visit 7

For detailed instructions on the collection, handling, labeling and shipment of samples please refer to separate Laboratory Protocol and Laboratory Manual.

All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

The exact clock time of dosing, as well as actual sample collection date and time (including pre-dose samples) will be entered on the appropriate page of the eCRF. Sampling problems will be noted in the relevant field of the eCRF.

When the assessments are scheduled to be performed at the same time-point, the order of priority will be as follows: questionnaires, ECG, vital signs, blood samples, imaging

biopsy and dosing.

Part A

Sampling windows

- For samples drawn on Day 1, there is a ± 15min window.
- For samples drawn after Day 1, there is a ± 6-hour window (based on T=0 dosing start time).

Visit windows

- From Day 1 to Day 14 visits should be conducted as scheduled.
- From Day 15 to Day 28 there is a ± 3 day visit window.
- From Day 33 (day of surgery) to EOS (end of study) there is a ± 5 day window.

Part B

Sampling windows

- For samples drawn on Day 1 there is a ± 15min window.
- For samples drawn after Day 1, there is a ± 6-hour window (based on T=0 dosing start time).

Visit windows

- From Day 1 to Day 15 visits should be conducted as scheduled.
- From Day 15 to Day 28 there is a ± 3 day visit window.
- From Day 57, Day 169 there is a ± 5 day window.
- For all follow-up visits until End Of Study visit, there is a ± 8 days window.

Part C

Sampling windows

- For samples drawn on Day 1 there is a ± 15min window.
- For samples drawn after Day 1, there is a ± 6-hour window (based on T=0 dosing start time).

Visit windows

- From Day 1 to Day 15 visits should be conducted as scheduled.
- Day 15 and Day 28 there is a ± 3 day visit window.
- From week 8 (Month 2 visit) to week 28 (Month 7 visit) there is a ± 5 day window.
- At week 12 visit, the ± 5 days window allows the site to perform week 12 MRI and receive information on potential dose escalation before planned dosing day.
- For all follow-up visits until End Of Study visit, there is a ± 8 days window.

Patients who prematurely withdraw from the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit 777 will be performed.

6.1 Dietary, fluid and other restrictions

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

- No strenuous unaccustomed physical exercise (e.g., weight training, aerobics, football) for 7 days before dosing until after Study Completion evaluation.
- No alcohol for 48 hours before and after dosing, and only for Part A, until 1 week after surgery. Also alcohol should not be consumed on the day or the day before assessment visits.
- Patients should not consume unpasteurized milk / milk products.

On day of surgery local guidance should be followed.

6.2 Patient demographics / other baseline characteristics

6.2.1 Demographics

Subject demographic and baseline characteristic data to be collected on all patients include: date of birth, sex, race, predominant ethnicity, height and weight.

6.2.2 Relevant medical history / Current medical conditions

Relevant medical history and current medical conditions will be recorded on the in the CRF until the start of the study drug (in Part C: until signing of the informed consent). Where possible, diagnoses and not symptoms will be recorded. **Diagnosis of PVNS and its date should be recorded, along with the description of the tumor (diffused or localized), number of relapses, location of relapse with dates, previous surgeries related to PVNS (number and type of open synovectomies or arthroscopies), medical treatments and radiation therapies.** Any event or change in the patient's condition or health status occurring ***prior to*** the start of the study drug (Part A and B) and prior to Informed Consent (Part C) will be reported in the Relevant medical history/Current medical conditions section of the CRF.

6.2.3 Hepatitis screen, HIV screen

History or serological evidence of HIV infection, hepatitis B or C infection (positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result) will lead to patient's exclusion from the study.

All patients aged 12-17 years old should be interviewed about the history of HIV, HepB and HepC infections and the outcome should be documented in the patient's source documents. Lab results, if available, should be included to source documentation.

All patients aged ≥18 years will be screened for Hepatitis B surface antigen (HBsAg). Screening for Hepatitis C will be based on HCV antibodies.

Evaluation for HIV seropositivity will be performed for all patients ≥18 years old, and, if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot.

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

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

6.2.4 Alcohol test, Drug screen

Patients will be tested for substances of abuse (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates).

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

6.2.5 Tuberculosis test

History or serological evidence of active or latent tuberculosis (TB) as indicated by a positive QuantiFERON or PPD skin test at screening will lead to patient's exclusion from the study.

6.2.5.1 QuantiFERON-TB Gold assay

A QuantiFERON®-TB Gold assay will be performed to assess the tuberculosis (TB) status at baseline of all adult patients (≥ 18 years old).

This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin vaccination or exposure to other Mycobacteria species.

This test, in contrast to the PPD skin test, is also insensitive to a booster effect since the patient is not exposed to the vaccine. The assay measures the production of interferon-gamma and puts it into relation to a negative and a positive control sample. QuantiFERON®-TB Gold assays will be provided by the central lab.

6.2.5.2 PPD skin test

A purified protein derivative (PPD) skin test will be performed for Part C patients aged ≥12 and <18 years old. This method does not require a blood draw.

The PPD skin test will be performed and will be read at Screening in order to evaluate an eventual infection with tuberculosis (TB). The test dose is bioequivalent to 5 tuberculin units (or as according to local standard practice) of standard PPD injected intradermally into usually the volar surface of the forearm. The site is cleansed and the PPD extract is then injected into the most superficial dermal layer of the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration) will take 48-72 hours to develop, the patient must return to the investigators' site within that time for a proper evaluation of the test site. This will determine whether the subjects have had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site. A PPD skin induration ≥ 5 mm is interpreted as positive result.

6.3 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all patients treated with MCS110 as detailed in Section 6.7.

6.4 Efficacy / Pharmacodynamic assessments

6.4.1 Tumor Volume by MRI

Collection and processing

MRI of the joints with PVNS will be taken during the screening phase. MRI scans have to be scheduled so, that a validated reference MRI should be available within 8 days before patient dosing (Part A and B).

For Part C, a validated reference MRI should be available within 3 weeks before patient randomization. This will allow for the evaluation of the image quality and measurability of tumor sizes. For screening and follow up MRI radiologists should schedule two appointments with the patient with a window of two days to account for a potential rescan.

If this MRI is not validated, a second MRI should be planned to get a validated reference MRI during screening period.

At visits including treatment administration, MRI should be scheduled within 5 days before MCS110 dosing day.

In Part C, at week 12, dose decision point, the MRI should be planned in a sufficient time before dosing day (at least 5 working days) to allow tumor volume evaluation and decision making on potential dose escalation.

All MRI scans will be transferred to the Imaging CRO (ICRO) electronically to determine if the images are of good quality without artifacts and to be reviewed by a central radiologist to confirm that the patient has at least one target lesion of measurable tumor size at screening, with minimum lesion dimension of at least 4 times the slice thickness and no less than 10 mm in the longest axis. If the images are not of good quality and/or not measurable, the ICRO will inform Novartis and the clinical sites within 48 hours and will request a new scan. If acceptable, the ICRO will also inform Novartis and the clinical sites and this will be considered as the validated reference MRI. The MRI image is read by two independent readers, for all scans at all time-points. The RECIST value for the Overall Best Response is taken as the value provided by the first reader. If the values between two readers do not match for overall best response this should be queried by data management and the readers should meet to reach consensus. In addition readers should meet to reach consensus if there is discrepancy in the number of lesions observed.

The MRI's will be carried out in accordance with the following specifications. The MRI protocol will use a core set of pulse sequences to optimize pathology, resolution and signal to noise (SNR) (Eckhardt and Hernandez 2004; Frick et al 2007; Cheng et al 2004). To ensure compatibility, the same scans, equipment, method, technique and scanning parameters used at screening will be used consistently throughout the study. Each scanner platform may have slightly different technical specifications depending on vendor and scanner type. Images will be acquires by strictly following the image acquisition guideline provided by the ICRO.

The general guidelines are as follows:

- All efforts must be made to ensure patient is comfortable during scanning.
- Ensure full coverage of the PVNS masses with the minimum possible field of view (FOV).
- Maximum signal to noise ratio (SNR).
- Minimum artifacts from patient motion and aliasing.
- Minimum matrix size of 256x192 and maximum slice thickness of 4 mm.
- A combination of T2, Proton Density (PD) and T1weighted image in two planes, 3D gradient echo (GRE) will be used to optimize pathology, resolution and SNR.
- Dedicated coils (such as, extremity coils for the knee and pelvic or torso coils for the hip) will be preferred over body coils.

The MRI scanning techniques and acquisition parameters will be provided to all clinical sites in an image acquisition guideline, developed for the study by a participating ICRO.

Analytical method

MRI scans will be transferred securely to the Imaging CRO (ICRO). The images will be evaluated by an experienced radiologist and a technologist of the ICRO to determine the image quality. If acceptable, the images will be analyzed for tumor volumes using software tools developed for automated or semi-automated measurements of structures in MRI (Ng et al 2010; Ashton et al 2001; Ashton et al 2003). The tumor boundaries will be identified by the ICRO technologist and reviewed by the central radiologist. All structural measurements will be

extracted in an automated fashion. Tumor volumes will be calculated by counting the total number of voxels contained within each defined boundary of the tumor and multiplied by the known volume of a single voxel.

6.4.3 Joint range of motion

Collection and processing

Range of motion (ROM) describes how much movement exists in a joint. Passive joint ROM will be assessed using a goniometer and degrees of flexion and extension from 90 degrees (Gerhardt 1983) will be noted in the eCRF. For example, if the patient can flex from 90º to 53º, the investigator will record 53º for flexion; if the patient can extend from 90º to 165º, the investigator will record 165º for extension.

Analytical method

Not applicable.

6.4.4 Joint specific questionnaires – KOOS (knee), SPADI (shoulder) and PREE (elbow)

During this study the following joint specific questionnaires will be completed by the patient depending on PVNS tumor location:

- KOOS (Knee and Osteoarthritis Outcome Scale) questionnaire for a PVNS tumor located in the knee
- SPADI (Shoulder Pain and Disability Index) questionnaire for a PVNS tumor located in the shoulder
- PREE (Patient Rated Elbow Evaluation) questionnaire for a PVNS tumor located in the elbow
- For other PVNS tumor location, no joint specific questionnaire will be dispensed to the patient.

Patients must complete the questionnaires before other clinical assessments at any given visit. Investigational staff will not influence, through verbal or other attitudes, the completion of self-administered questionnaires.

Completed questionnaires will be reviewed and examined by the investigator before the clinical examination for responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient.

If the occurrence of AEs or SAEs is confirmed, the physician must record the events as per instructions given in Section 7.2 of the protocol. Investigators should not encourage the patients to change the responses reported in the Patient-Reported Outcome (PRO) questionnaires.

6.4.5 Pain assessment using visual analog scale (VAS)

During the study, patient's pain will be assessed with a 100 mm visual analog scale (VAS). The pain VAS will be completed by the patient at determined clinical visits, as per the assessment schedule. In addition, the patients should record their pain assessment at home, on a daily basis for 14 days following the first treatment - by completing a Pain VAS Patient Diary provided by the site. The patient will be asked to place a line perpendicular to the VAS line at the point that represents his/her pain intensity.

Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the "no pain" anchor and the patient's mark, providing a score from 0-100.

The VAS is administered as a paper and pencil measure. As a result, it cannot be administered verbally or by phone. No training is required other than the ability to use a ruler to measure distance to determine a score. Caution is required when photocopying the scale as this may change the length of the 10-cm line as slightly lower scores have been reported. The scores for the site visits and also the patient diary will both be captured in the CRF.

6.4.6 Total M-CSF concentration in plasma and synovial fluid (if available)

Total M-CSF levels will be measured in plasma to evaluate the PD effect of MCS110. Blood samples for the analyses of total M-CSF will be collected during the study from all patients. In addition, total M-CSF levels will be measured in synovial fluid collected during the surgery from all Part A patients and patients who will undergo arthroscopy or surgery in Part B and Part C.

Part A only: If changes are observed in total M-CSF plasma concentrations, patients will be followed up until their total M-CSF concentrations return back to baseline.

6.4.7 Mode of action biomarkers

Fasting blood samples for these assessments must be taken in the early morning. The time of collection should be noted on the biomarker shipping form.

6.4.7.1 Cellular biomarkers

Only Part A and Part B:

Blood samples will be collected for the evaluation of CD14+ monocytes and CD14+CD16+ monocytes by FACS. Based on preliminary results, the quality of the samples did not allow to draw a meaningful conclusion and data will not support the achievement of the clinical objective. Thus, in Part B the monocytes samples collection will be discontinued.

6.4.7.2 Serum soluble form of sCSF-1R

The effect of MCS110 on sCSF-1R will be assessed in serum.

6.4.7.3 Serum bone biomarkers

Biomarkers of bone resorption (CTX-I) Corporate Confidential Information will be performed in serum to assess changes in bone metabolism.

6.5 Safety

6.5.1 Physical examination (including index joint ROM)

A complete physical examination will include the examination of general appearance, skin (including evidence of edema in the legs, hands, and face), neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. The range of motion in the index joint will also be evaluated.

Information for all physical examinations must be included in the source documentation at the study site and will not be recorded the eCRF. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's eCRF.

The occurrence of periorbital swelling and if possible, edema and any dermatological changes should be documented with photography. In case of dermatological changes a skin biopsy should be taken, if feasible.

Index joint range of motion (ROM) as assessed under Section 6.4.3.

6.5.2 Vital signs

During the infusion vital signs will be monitored every 15 minutes with a ± 5 minute window.

Vital signs include BP and pulse and body temperature measurements. After the patient has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

If vital signs are out-of-range at screening and baseline, the Investigator should obtain two additional readings**,** so that a total of three (3) consecutive assessments are made, with the patient seated quietly for approximately five (5) minutes preceding each repeat assessment. ***At least the last reading must be within the ranges provided above in order for the patient to qualify.***

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

6.5.4 Laboratory evaluations

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a **protocol-specified range** at screening and/or at the initial baseline, the assessment may be repeated once (for the purpose of inclusion), and in any case, prior to enrollment/randomization, to rule out laboratory error. If the repeat value remains outside of protocol-specified ranges, the patient should be excluded from the study.

In the case where a laboratory range is **not specified by the protocol**, but is outside the reference range for the center at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once (for the purpose of inclusion) and in any case, prior to enrollment/ randomization, to rule out laboratory error.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the patient to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

6.5.4.1 Hematology

Complete blood count consisting of red blood cell (RBCs), a total white blood cell count with differential (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), hemoglobin and platelet count.

The above parameters results should be available locally before dosing to verify hematology profile of the patient.

6.5.4.2 Coagulation

Only for patients ≥18 years old: The coagulation profile includes a prothrombin time (PT) or international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen. The assessments must be performed by the central lab along with the standard hematology assessments.

The above parameters results should be available locally before dosing to verify coagulation profile of the patient.

6.5.4.3 Immunoglobulins (IgA, IgE, IgG, IgM)

For total immunoglobulin measurements, assessment of total serum IgG, IgG subclasses, IgM, IgE and IgA and will be performed by the central lab with the standard hematology assessments. If immune parameters are abnormal at end of treatment and are considered clinically significant, patients must be followed monthly until values have returned to baseline or until 6 months after the last dose and at the discretion of the Investigator.

6.5.4.4 Clinical chemistry

If needed to verify postmenopausal status, a FSH test will be performed at screening (Visit 1).

Aldolase, albumin, alkaline phosphatase, total bilirubin (direct and indirect), calcium (total and ionized), cholesterol (total cholesterol, HDL cholesterol, LDL cholesterol), high sensitivity C-reactive protein (hsCRP), creatinine (including calculation of GFR), CK, γ-GT, glucose, IL-6, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, PTHrP, sodium, triglycerides, urea or BUN and uric acid will be assessed.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

The clinical chemistry results (same as above except IL-6, PTHrP and aldolase) should be available locally before dosing to verify clinical chemistry profile of the patient.

For patients 12-17 years old PTHrP, aldolase and fasted plasma glucose are not required.

6.5.4.5 Muscle enzymes

Cardiac troponin-T (cTnT), creatine kinase (CK) and the MB isoenzyme of CK (CK-MB) will be assessed by the central lab along with the standard clinical chemistry assessments.

The cTnT or cTnI parameters results should be available locally before dosing to verify profile of the patient.

For patients 12-17 years old cTnT testing is not required.

6.5.4.6 Urinalysis

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

A semi-quantitative "dipstick" evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes and blood.

A "dipstick" evaluation should be available locally before dosing.

If the dipstick result is positive for protein leucocytes or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

6.5.5 Pregnancy

Pregnancy tests are required of all female patients regardless of reported reproductive / menopausal status. Serum pregnancy tests will be performed at screening and at End of Study at all other times urine pregnancy tests may be used. The result of this test must be received before the patient is dosed.

6.5.6 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed. Interpretation of the tracing must be made by a qualified physician and documented on the ECG section of the eCRF. Each ECG tracing should be labeled with the following and kept in the source documents at the study site:

- study number
- patient initials
- patient number
- date and time

Only clinically significant abnormalities should be reported on this page. Clinically significant abnormalities should also be recorded on the relevant medical history/Current medical conditions eCRF page. Clinically significant findings must be discussed with the sponsor. The clock on the ECG machine should be synchronized with the central clock on a daily basis. The eCRF will contain:

- date and time of ECG
- heart rate
- PR interval
- QT interval (uncorrected)
- QTcF
- QRS duration

The overall interpretation will be collected with a Yes/No statement to confirm if any clinically significant abnormalities are present which need to be specified further.

Original ECG tracings, appropriately dated and signed, will be archived at study site.

6.5.8 Meal record

Not applicable.

6.6 Pharmacokinetics and Immunogenicity

Blood samples for the analyses of pharmacokinetics (PK) and immunogenicity of MCS110 will be collected during the study from all patients. In addition, synovial fluid samples for the analysis of MCS110 concentration will be collected, if possible, from patients who may undergo surgery.

6.6.1 Analytical methods

The detailed method descriptions of the PK and Immunogenicity assays will be included in the corresponding bioanalytical data reports.

6.7 Other assessments

Corporate Confidential Information

6.7.2 Health-related quality of Life (mHAQ and EQ-5D)

During this study the following questionnaires will be utilized mHAQ and EQ-5D for quality of life. Patients must complete the questionnaires before other clinical assessments at any given visit. Investigational staff will not influence, through verbal or other attitudes, the completion of self-administered questionnaires.

Completed questionnaires will be reviewed and examined by the investigator before the clinical examination for responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient.

If the occurrence of AEs or SAEs is confirmed, the physician must record the events as per instructions given in Section 7.2 of the protocol. Investigators should not encourage the patients to change the responses reported in the Patient-Reported Outcome (PRO) questionnaires.

Corporate Confidential Information

7 Safety monitoring

7.1 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events eCRF with the following information:

- the severity grade (mild, moderate, severe)
- its relationship to the study drug(s) (suspected/not suspected)
- its duration (start and end dates or if continuing at final exam)
- whether it constitutes a serious adverse event (SAE)

A SAE is defined as an event which:

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

Any required in patient hospitalization after day 33 surgery to complete PVNS tumor resection will not be considered as a serious adverse event.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.2 Serious adverse event (SAE) reporting

Any required in patient hospitalization after day 33 surgery to complete PVNS tumor resection will not be reported as a serious adverse event (only for Part A).

Any required patient hospitalization due to surgery to complete PVNS tumor resection will not be reported as a serious adverse event (for Part B and C).

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship of any SAE to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Chief Medical Office & Patient Safety Department. The telephone and telecopy number of the contact persons in the local department of Clinical Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe

whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Chief Medical Office & Patient Safety Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Pregnancies

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. When pregnancy occurs in a patient in the study, the **study drug must be discontinued**. The occurrence of pregnancy will trigger unblinding of a given patient (see Section 14.1) for safety purposes. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The collection of this information could last for up to 3 months following the birth of the child. Similar information will be collected if the partner of a male participant become pregnant while her partner is participating to the study.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office & Patient Safety Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.4 Data Monitoring Committee

Not applicable.

8 Data review and database management

8.1 Site monitoring

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

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical

information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRF are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

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

8.3 Database management and quality control

CRO staff on the behalf of Novartis will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. No obvious corrections are allowed for this study. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

- Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.
- Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.
- Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).
- MRI data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

At the conclusion of a non-IVRS study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis. The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Clinical Information Sciences and the Clinical Franchise Head.

9 Data analysis

9.1 Analysis sets

All patients as randomized that received at least one dose of study drug will be included in the data analysis. Patients will be analyzed according to the treatment actually received - "all patients population".

For patients for which the actual treatment received does not match the randomized treatment the treatment actually received will be used for the analysis.

All patients that received study drug and with no protocol deviations with relevant impact on safety will be included in the safety analysis set.

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

The PD analysis set will include all patients with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

9.2 Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by study part and patient. For these parameters summary statistics will be provided accordingly.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by study part and patient.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Study drug, other concomitant therapies, and compliance will be listed by study part and patient.

9.4 Analysis of the primary variable

9.4.1 Variable(s)

Part A:

The tumor size (volume) as assessed by MRI technique up to and including week 4 will be the primary measure of efficacy. The tumor size at baseline and at week 4 will be log transformed. The log ratio to baseline of the tumor size (change from baseline of log transformed volume) will be the primary endpoint.

Part B:

The tumor volume will continue to be the primary measure of efficacy. In particular, if the tumor is too small to be measurable at follow-up, it is considered as complete response.

Part C:

The tumor volume will continue to be the primary measure of efficacy. In particular, if the tumor is too small to be measurable by MRI, it is considered as complete response.

Tumor volumes will be listed and descriptively summarized at each MRI assessment time by MCS110 dose group (3 mg/kg, 5 mg/kg, 10 mg/kg). Moreover, the number and percentage of patients with complete tumor response (CR) will be presented, and the time that the complete tumor response is observed will be listed by patient and dose group. In addition, incidences of patients with partial response (PR), stable disease (SD) and progressive disease (PD) will be listed by dose group.

Tumor volume reduction after 3 doses, evaluated by week 12 MRI, will guide the decision on whether to continue with the initial dosing (3 mg/kg or 5 mg/kg) or increase the dose to 10 mg/kg for the following doses.

9.4.2 Statistical model, hypothesis, and method of analysis

Part A:

The analysis of the primary endpoint will quantify the accumulation of evidence about the treatment effect as patients complete their 4 week treatment. The evidence will be summarized in the posterior distributions of the treatment group means and their differences. These posterior distributions will be updated after each patient completes the 4 week treatment.

For the analysis, the distributional model for the observed data (log ratio) will be the normal model with unknown parameters μ and σ, with μ being the parameter of primary interest (treatment mean) and σ representing the sampling error. Little prior information is available for these parameters and therefore non-informative prior distributions will be placed on them. For μ a normal prior distribution centered at 0 (no treatment effect) will be used with large standard deviation, and for σ a uniform (0,2) prior distribution.

The model is formally described below, LR being the log ratio of tumor volume:

Likelihood

$LR_i \sim N(\mu, \sigma)$

with

$\mu = \mu_p$ for observations from placebo group

$\mu = \mu_m$ for observations from MCS110 group

Prior distributions on treatment means μ's

$\mu_p \sim N(0, 0.3)$

$\mu_m \sim N(0, 10)$ * i.e., Neutral prior or

$\mu_m \sim N(0, 0.3)$ * i.e., Skeptical prior

Prior distributions on sigma

$\sigma \sim$ Uniform (0,2)

Decision Rule

The PoC criterion is two-fold, as follows:

1. Prob(LR(treated) < LR(placebo)) > 0.90; i.e., 90% confidence in superiority to placebo
2. Prob(LR(treated) - LR(placebo) < log(0.6)) > 0.50; i.e., 50% confidence in the treated group ratio being 40% below the placebo group ratio

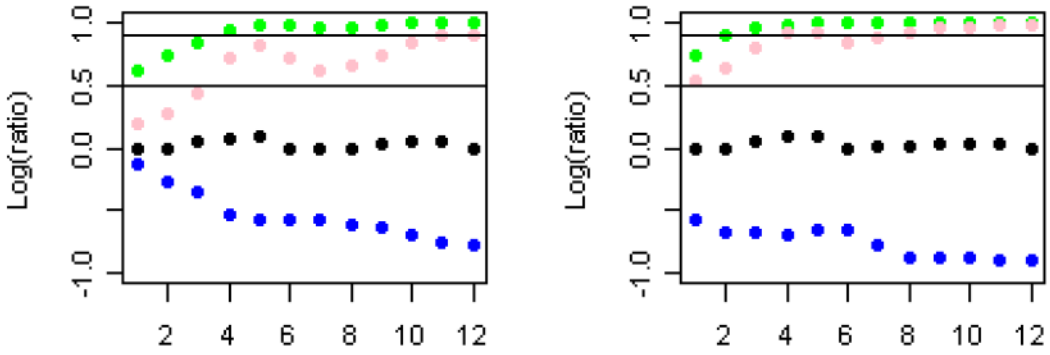
At least one placebo patient and two MCS110 patients must be included to declare PoC. Both neutral and skeptical priors will be used to assess the PoC criterion. The skeptical prior is used to shift prior beliefs toward no effect of MCS110, i.e., stronger evidence from the data in favor of MCS110 will be needed to reach PoC. The skeptical analysis will only be run as a sensitivity analysis.

Once the PoC criterion is reached, the clinical trial team (CTT) may decide to continue recruitment to collect more data on MCS110.

If after 6 patients have completed the 4 week treatment, the PoC criterion is not reached, the probability to reach PoC with the addition of 6 new patients will be assessed, and if this probability is less than 10% the trial may be stopped for futility.

For illustration, an example of a trial path simulation with skeptical and neutral priors on mean treatment effect in MCS110 group is shown below (Figure 9-1):

Figure 9-1 Example of a sample path



The left plot displays the skeptical analysis and the right plot the neutral analysis.

The blue dots represent the posterior mean in the MCS group and the black dots represent the posterior means in the placebo group as more patients contribute data.

The green dots show the probability of MCS110 being superior to placebo, and the pink dot the probability to be better by 40%.

In this example, the PoC criterion is reached after 3 patients when neutral prior (second graph) is used, and after 4 patients when skeptical prior (first graph) is used.

Part B:

Tumor volumes will be listed and descriptively summarized at each MRI assessment time by treatment groups (treatment group 1 = MCS110 throughout the trial, treatment group 2 = Placebo for the first dose and MCS110 from the second dose) accordingly. Moreover, the number and percentage of patients with complete tumor response will be presented, and the time that the complete tumor response is observed will be listed by patient and treatment group.

In addition, we may pool treatment groups by matching the 1st dose of MCS110 in treatment group 1 to the 2nd dose (1st of MCS110) in treatment group 2. More specifically, for treatment group 2, the measurement right before patients receiving the first dose of MCS110 (2nd dose from screening) will be treated as the new baseline and assessment time-points will be adjusted accordingly. This may apply to all analyses in Section 9 if necessary.

Part C:

Tumor volumes will be listed and descriptively summarized at each MRI assessment time by treatment arm (treatment arm 1 = MCS110 3 mg/kg, treatment arm 2 = MCS110 5 mg/kg, treatment arm 3 = MCS110 10 mg/kg) accordingly. Moreover, the number and percentage of patients with complete tumor response (CR) will be presented, and the time that the complete

tumor response is observed will be listed by patient and treatment arm. In addition, incidences of patients with partial response (PR), stable disease (SD) and progressive disease (PD) will be listed by treatment arm.

More specifically, for patients in treatment arms 1 and 2 that switch to 10 mg/kg after 3 doses, the measurement right before patients received the first dose of MCS110 10 mg/kg (4th dose from screening) will be treated as the new baseline and assessment time-points will be adjusted accordingly. This may apply to all analyses in Section 9 if necessary.

9.4.3 Handling of missing values/censoring/discontinuations

Patients who withdraw early will be replaced, as described in Section 5.5.9. The following two data sets may be analyzed separately: data set 1 will include all patients' data without any surgery throughout the trial; data set 2 will include data set 1 and patients' data prior to surgery. Data post-surgery will not be used for primary analysis.

9.4.4 Supportive analyses

Part A

As a supportive analysis, log ratio to baseline of tumor volume at week 4 may be subjected to an Analysis of Covariance (ANCOVA) model. The model will include log transformed tumor volume at baseline and a factor for treatment. Point estimates and 95% confidence interval will be calculated for each treatment group and for the difference of means between treatment groups. Results will then be transformed back to the original scale.

Part B

To study the time course of tumor volume reduction from baseline, a repeated measures ANCOVA model may be fit by resetting the tumor volume at week 4 as baseline for patients in treatment group 2 and the assessment time will be adjusted accordingly. The model will include tumor volume at baseline and assessment time (in month) as fixed effects. Standard fit statistics will be used to determine the best variance-covariance structure. Point estimates and 95% confidence interval will be calculated at each assessment time-point and between different assessment time-points.

Part C

As a supportive analysis, log ratio to baseline of tumor volume at week 4 may be subjected to an Analysis of Covariance (ANCOVA) model. The model will include log transformed tumor volume at baseline and a factor for treatment. Point estimates and 95% confidence interval will be calculated for each treatment arm and for the difference of means between treatment groups. Results will then be transformed back to the original scale.

Parts A, Part B and Part C

A basic dose-time-response model (Lange and Schmidli 2015) will be used to analyze tumor response data from Parts A, B, and C. Time-dose-response models describe and predict drug effect for complex dosing regimens. The mechanistic non-linear regression model used will allow for both inference on model parameters and prediction of the time-changing tumor response for the dosing regimens used in this study. Mechanistic models are based on prior knowledge and provide more reliable predictions. To this end, a Bayesian approach (using prior information) with weakly informative prior will be used. Point estimates and 95% confidence intervals of the model parameters, i.e., the expected response after multiple doses, will be generated using the Emax model. The Emax model will estimate tumor reduction from baseline at each dose and timepoint. Dose-time-response curves based on the model will be generated and graphically presented. The pooled dataset should result in approximately 19 patients on 10mg/kg, 6 patients each on 3 and 5 mg/kg (up to 10 if a lower efficacious dose is identified), and 5 patients (2 in Part A and 3 as first dose in Part B) on placebo.

9.5 Analysis of secondary variables

The first 4 weeks data from Part A, Part B, and Part C will be pooled together for analyses. In addition, data in Part B will be analyzed by treatment groups; we may also pool treatment groups by matching the 1st dose of MCS110 in treatment group 1 to the 2nd dose (1st of MCS110) in treatment group 2.

Part C analyses of secondary variables will be done by treatment group. We may also pool treatment groups across Parts B and C to analyze secondary variables.

9.5.1 Efficacy / Pharmacodynamic variables

Soluble form of M-CSFR (sCSF-1R), bone marker serum C-terminal Type I Collagen peptide (CTX-I) and monocytes (hematology) will be collected as specified in the study assessments schedule.

Summary statistics and graphical display of these parameters over time with the absolute values, and ratio from baseline will be produced. Total circulating M-CSF levels (if available) will be displayed graphically.

Summary statistics and graphical display of this parameter over time with the absolute values, and ratio from baseline will be produced by plasma and synovial fluid separately.

Joint range of motion

Summary statistics and graphical displays for the absolute values, absolute changes from baseline joint range of motion over time will be produced by flexion and extension separately and by each joint type.

Joint Specific Questionnaires

Data will be summarized and graphically displayed similarly by tumor locations.

Health-related quality of life

All data related to health-related quality of life including but not limited to EQ5D, mHAQ, will be summarized and graphically displayed similarly.

Pain assessment (VAS)

Pain assessment data will be summarized and graphically displayed similarly.

Time to surgery

Number of patients who receive surgery will be presented and their time to surgery will be listed and summarized accordingly.

Tumor relapse / re-growth

Number of patients who experience recurring PVNS tumor / tumor growth of residual tumor may be listed and their time to relapse /re-growth may be listed and summarized accordingly. The tumor size monitored by MRI will be recorded over time.

9.7 Safety

Vital signs

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

ECG evaluations

All ECG data will be listed by treatment, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Standard clinical laboratory evaluations

All laboratory data will be listed and graphically displayed by treatment, patient, and visit/time and abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Special clinical laboratory evaluations

All laboratory data will be listed by treatment, patient, and visit/time and if ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment and patient. The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. An adverse event starting in one period and continuing into the next period is counted only in the onset period. A patient with multiple adverse events within a body system /within a treatment period/ is only counted once towards the total of this body system.

Concomitant medications / Significant non-drug therapies

All concomitant therapies will be listed by treatment group and patient.

9.8 Pharmacokinetics

During modeling of the pharmacokinetics of the study drug, the broad principles outlined in the FDA Guidance for Industry: Population Pharmacokinetics will be followed.

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

While the serum free MCS110 concentration-time data will mostly be summarized graphically and analyzed using a model-based approach (which will be reported separately in a Modeling & Simulation report), noncompartmental pharmacokinetic analysis will also be performed and the following noncompartmental PK parameters characterizing the disposition of MCS110 will be generated using WinNonlin Phoenix® (Version 6.2 or above, Pharsight, Mountain View, CA):

- Part A: AUClast, AUCinf, Tmax, Cmax, CL, Vss, T1/2 and MRT.
- Part B: AUCτ (τ=dosing interval in Part B), Racc (accumulation ratio), Tmax, Cmax, T1/2.
- Part C: AUCτ (τ=dosing interval in Part C), Racc (accumulation ratio), Tmax, Cmax, T1/2.

Additional PK parameters may be determined and compartmental PK modeling may be performed where appropriate.

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the limit of quantification will be treated as zero in summary statistics and for the calculation of pharmacokinetic parameters.

Descriptive statistics of pharmacokinetic parameters will include mean, SD, and CV, min and max. When a geometric mean will be presented it will be stated as such. Since T_{max} is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter.

9.12 PK/PD

Individual serum/plasma concentration versus time profiles of MCS110, M-CSF and other PD biomarkers will be displayed graphically. In addition, PKPD modeling may be performed where appropriate.

The analysis of the relationship between drug concentration and PD variables will be data driven. Therefore, nature of analysis will depend on the type of data obtained in the study and it may be difficult to specify the analysis in advance. Drug concentration-PD data can be evaluated by a PK-PD model (such as target binding model, indirect response model, etc.) analysis if appropriate.

9.13 Sample size calculation

Part A

The trial will be analyzed after each patient has completed Day 28 visit and the tumor volume has been assessed by MRI. The trial may stop at any time if the PoC criterion (see Section 9.4.2) is met, and therefore no fixed sample size is planned. However, a maximum of 12 evaluable patients will be recruited, with a 2:1 ratio MCS110 to placebo. The minimum number of patients to declare PoC is 3, i.e., 2 MCS110 patients and one placebo patient.

Imatinib is known to inhibit the macrophage colony-stimulation factor receptor (CSF-1R). In a recent report it has been demonstrated, that imatinib treatment led to a partial response within 2 months of treatment and a complete response after 5 month of treatment in one case of advanced recurrent PVNS (Blay et al 2008). Given, that imatinib is not a particularly strong inhibitor of CSF-1R (Dewar et al 2005), treatment with an Ab against M-CSF, such as MCS110, which specifically blocks CSF1 signalling is expected to show a 40% reduction in one month.

From scan-rescan MRI reproducibility experiments (Ng et al 2010), it is expected to observe up to 10% variability in measurement of tumor size due to imaging techniques, parameters used, types of tumor (e.g., size or shape) or observers. Due to inter-occasional variability, and due to a potential inflation of variability in the presence of treatment, the actual within-subject variability may be bigger, i.e., the within subject variability in the MCS110 treated patients is assumed to be about twice as much, i.e., 20%. For the placebo patients both 10% and 20% variability assumptions are considered. As a very conservative scenario, we assume also a 30% variability in both groups.

This leads to 3 possible scenarios:

- Scenario 1: 10% within subject variability for the placebo patients and 20% for the MCS110 patients.
- Scenario 2: 20% within subject variability for the placebo and MCS110 patients
- Scenario 3: 30% within subject variability for the placebo and MCS110 patients

Assuming the treatment/placebo effects to be identical in all patients, the residual error of the log ratio relative to baseline is then approximately 0.1 * sqrt(2) or 0.2 * sqrt(2) or 0.3 * sqrt(2), depending on group/scenario.

Given these scenarios, the table below (Table 9-1) summarizes the power of the study obtained by simulations of 800 trials with 4 different sample sizes.

Table 9-1 Power estimates for different scenarios

N patients	Scenario 1	Scenario 2	Scenario 3
12	95%	89%	82%
9	90%	85%	79%
6	88%	83%	74%
3	69%	62%	46%

In scenario 1, with 12 patients and assuming a twofold reduction from baseline in tumor size in the MCS110 group as compared to the placebo group, there is about 95% power to reach the PoC criteria as defined above in the analysis section. With 6 patients (4:2), the power is about 88%.

In Scenario 1, the probability to declare a positive PoC when there is no treatment difference is less than 0.6% at each analysis. Therefore the overall type 1 error rate is bounded at 6% (maximum of 10 analyses). In Scenario 2, the overall type 1 error rate is bounded at 9% and in Scenario 3 bounded at 35%.

Part B

There are anticipated to be about 12 patients in Part B (18 in total for this trial). The following table (Table 9-2) presents the 95% Confidence Interval (CI) for the true proportion of patients with complete tumor response, assuming different proportions of patients with complete tumor response are observed.

Table 9-2 95 percent confidence intervals for the proportion of complete response

$\hat{p}$*	0/12 (0)	1/12 (0.08)	2/12 (0.17)	3/12 (0.25)	4/12 (0.33)	5/12 (0.42)	6/12 (0.5)
95% CI	(0, 0.22)	(0.002, 0.38)	(0.02, 0.48)	(0.05, 0.57)	(0.1, 0.65)	(0.15, 0.72)	(0.21, 0.79)

$\hat{p}$	7/12 (0.58)	8/12 (0.67)	9/12 (0.75)	10/12 (0.83)	11/12 (0.92)	12/12 (1.00)
95% CI	(0.28, 0.85)	(0.35, 0.90)	(0.43, 0.95)	(0.52, 0.98)	(0.62, 1)	(0.78, 1)

*Note: $\hat{p}$ is the observed proportion of patients with complete tumor response. The proportion is also converted into two decimal places shown in the parenthesis.

Part C

There are anticipated to be 19 patients in Part C (approximately 37 patients in total for the trial). Simulations run using prior study information, log (ratio) of tumor size, and a conservative standard deviation estimate, show that 6 patients per arm in the 3 and 5 mg/kg groups will provide >80% power to declare the lower doses efficacious or not, compared to the 10 mg/kg group.

9.14 Power for analysis of key secondary variables

Not applicable.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). For adolescent patients, written informed consent is required from the legal representative and the adolescent must assent to participation. The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Corporate Confidential Information

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or ethics committee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form Corporate Confidential Information must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is

requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

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14 Appendix 2: Blinding and Unblinding

14.1 Part A and first dose Part B

This is a double-blind placebo-controlled PoC study. Unblinding is permitted for the statistician and programmer on a patient by patient basis, once a patient has reached 4-weeks post-dose.

Unblinding may also take place when an interim analysis is conducted or an event of concern (such as a clinically significant out of normal range laboratory assessment) is encountered for a single patient. Processes and levels of unblinding are indicated in Table 14-1.

Table 14-1 Blinding levels and processes for PoC study

	Time or Event						
People Allowed to be unblinded (U)	1	2	3	4	5	6	7
Drug Supply	U	U	U	X	X	U	U
Randomization Office	U	B	B	X	X	U	U
Patient	B	B	B	X	X	B	U
Treating Physician	B	B	B	X	X	B	U
Primary Investigator	B	B	B	X	X	B	U
Study monitor	B	B	B	X	X	B	U
Clinical Trial Leader	B	B	B	X	X	U	U
Data management	B	B	B	X	X	B	U
TME	B	B	B	X	X	U	U
Independent Safety Reviewer	B	B	B	X	U	U	U
BAPK	B	B	U	U	U	U	U
BMD	B	B	B	U	U	U	U
Pharmakokineticist	B	B	B	X	X	U	U
Statistician	B	B	B	X	X	U	U
Modeler*	B	B	B	X	X	U	U
Programmer	B	B	B	X	X	U	U
Interim Analysis: Statistician / Modeler* / Programmer	B	B	B	X	X	U	X
Independent Statistician(s) (only Part C)	B	B	U	U	U	U	U
Independent safety reviewer (only Part C)	B	B	U	U	U	U	U

U Allowed to be un-blinded
B Remains blinded
X Not applicable
1 Generation of Randomization List, QC and lock randomization list
2 Patient Allocation
3 Patient administration
4 period finalization (initiation of next dose group per protocol decision)
5 event of concern (individual un-blinding)
6 Interim analysis
7 Database Lock

The Study monitor notifies the Clinical Leader when a milestone has been reached according to the predefined un-blinding procedure as indicated in the table shown above.

The Clinical Leader notifies the Biostatistics Quality Assurance Randomization Officer in writing. Unblinding can then be initiated according to the predefined unblinding procedure for the study protocol. BQA Randomization Office will make the treatment allocation information available to the authorized personnel.

Review and analysis of the unblinded data will become part of the FIR for this study.

14.2 Part B – Open label

Part B first dose double blind is followed by an open-label study part. All study team members, all personnel staff and patients will be un-blinded from the second dose to the last dose.

Only day 1 treatment allocation will remain double blinded to all study team members, all personnel staff and patients until week 12.

At week 12, Part B first dose will be un-blinded to study team, personnel staff and patients in order to allow first dose placebo patient to receive a fourth MCS110 dose following Assessment Schedule Part B1.

14.3 Part C

Study Part C double blind treatment part is followed by an open-label study part. Day 1 treatment will be maintained double-blinded until Week 28 to the Novartis clinical team and the investigator. All study team members, all personnel staff, and patients will be unblinded after the Week 28 completion for each patient.

At Week 12, Novartis independent statistician will proceed to the un-blinding and will share allocated dose level with an independent unblinded Novartis medical person who will review patient's safety profile and tumor volume reduction. The unblinded medical person will determine if the patient fulfills dose change conditions. The site's unblinded pharmacist will be informed by an independent study team member of potential dose change.