HELSE BERGEN
Haukeland universitetssjukehus

Clinical Trial Protocol

Randomized Autologous heMatopoietic stem cell transplantation versus Alemtuzumab for patients with relapsing remitting Multiple Sclerosis

Protocol Identification: RAM-MS

EudraCT Number: 2017-001362-25

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PROTOCOL VERSION NO. 4.2, 20-Dec-2017

SIGNATURE PAGE

Title **Randomized autologous hematopoietic stem cell transplantation versus Alemtuzumab for patients with relapsing remitting Multiple Sclerosis**

Protocol ID no: **RAM-MS**

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I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Role	Signature	Date
Håkon Taule Nordli	Department head	Sponsor representative		
Lars Bø	Consultant neurologist/ professor	Coordinating Investigator		

PROTOCOL SYNOPSIS

Randomized autologous hematopoietic stem cell transplantation versus Alemtuzumab for patients with relapsing remitting Multiple Sclerosis

Sponsor:	Helse Bergen HF, Haukeland University Hospital Håkon Taule Nordli Neuro Clinic N-5021, Bergen, Norway Tel :55975857
Phase and study type:	Phase III, interventional
Protocol date and version: Protocol Revision date and version:	20-Dec-2017, version 4.2 NA
Investigational Medical Product (IMP):	Study treatment **arm A**: Cyclophosphamide and anti-thymocyte globuline Study treatment **arm B**: Alemtuzumab
Objectives:	The objective of this study is to investigate the efficacy and the safety of HSCT, compared to alemtuzumab in patients with aggressive relapsing remitting MS.
Study Design:	Prospective multicentre, interventional, unblinded, randomized, parallel group study
Number of patients:	Approximately 100 patients, 50 in each treatment arm.
Study duration:	Estimated date of first patient enrolled: 01-Jan 2018. Anticipated recruitment period: 2 years 2 years follow-up from Treatment day “0” (baseline) in both arms. Estimated date of last patient completed: 31-December-2021
Follow-up duration:	A pre-planned study extension with additional 3 years follow-up may be conducted depending on future funding.
Treatment administration:	Arm A: mobilization and harvesting; 10 days, conditioning and reinfusion; 6 days. Arm B: At start of treatment; infusion for 5 consecutive days, and 1 year later; infusion for 3 consecutive days

Main Inclusion Criteria:	○ Age between ≥18 to ≤50, both genders ○ Diagnosis of RRMS using revised McDonald criteria of clinically definite MS[1] ○ An EDSS score of 0 to 5.5 ○ Significant inflammatory disease activity in the last year despite treatment with standard disease modifying therapy (interferon beta, glatiramer acetate, dimethyl fumarate, teriflunomide, fingolimod, natalizumab) ○ Significant inflammatory disease activity is defined by: ➢ One or more clinically reported multiple sclerosis (MS) relapse(s), ➢ AND 1 or more T_1 Gd-enhanced lesion(s), ➢ OR three or more new or enlarging T_2 lesions on magnetic resonance imaging (MRI) The relapse(s) must have been treated with iv or oral high dose corticosteroids prescribed by a neurologist, and must have occurred 3 or more months after the onset of an immunomodulatory treatment, as MS immunomodulatory treatment may reach full effect after 3 months or more[2].
Endpoints:	**Primary endpoint:** The primary efficacy endpoint is to determine differences between patients in the 2 treatment arms according to the following criteria: • Proportion of patients with no evidence of disease activity (NEDA, as defined per protocol) during a 2 year (96 week) period • Pre-planned study extension: Proportion of patients with NEDA (as defined per protocol) during a 5 year (240 week) period. NEDA is the absence of a protocol defined disease activity event. A protocol-defined disease activity event is the occurrence of at least one of the following: - A new T_1Gd-enhanced lesion on MRI of the brain and spinal cord - A new T_2 hyperintense lesion on MRI of brain and spinal cord - A protocol-defined MS relapse (see definition below) - 24 week confirmed disability progression based on increases in Expanded Disability Status Scale (EDSS) (see definition below and Appendix C) MS relapse is defined as new or worsening neurological symptoms attributable to MS, lasting at least 48 hours, without pyrexia, after at least 30 days of clinical stability with an objective change on neurological examination[3]. Disability progression is defined as an increase of one point in the EDSS score (or half

	a point if the baseline EDSS score was equal to 5.5), confirmed after 24 weeks, with an absence of relapse at the time of assessment. MRI imaging will be performed according to the Revised Consortium of Multiple Sclerosis Centers (CMSC) MRI Protocol and Guidelines[4] **Secondary endpoints:** The secondary efficacy endpoint for this study is to evaluate the efficacy of the study treatments on the basis of the following endpoints: • Proportion of patients who have no evidence of disease activity, including atrophy (NEDA 4), as per protocol defined disease activity events (as defined in section 2.2) plus atrophy (measured yearly atrophy above threshold of 0, 4 %) during a 2 year (96 week) period[5]. o Pre-planned study extension: Proportion of patients who have NEDA 4 during a 5 year (240 week) period. • Time to first protocol-defined disease activity event as defined in section 2.2 • Change in EDSS from baseline (Visit 4.1) to Weeks 96 and 240 • The proportion of patients who, at Week 96, have protocol-defined Confirmed Disability Improvement (CDI) , confirmed stable EDSS or Confirmed Disability Progression (CDP) compared to baseline • Annualized rate of protocol-defined relapses during 96 weeks • Time to onset of first protocol-defined relapse • Change in MRI T_2-weighted hyperintense lesion volume from baseline to Weeks 48 and 96 (and 240) • Change in MRI T_1-weighted hypointense lesion volume from baseline to Weeks 48 and 96 (and 240) • Change in brain volume from baseline to week 48 and week 96 (and week 240), and from week 48 to week 96 (and week 240)[5] • Time to detection of a new MRI T_2 lesion • Total number of MRI T_1-weighted Gd-enhanced lesions at weeks 24, 48, 96 (and 240) • Proportion of patients free from T_1 Gd-enhancing lesions at weeks 24, 48, 96 (and 240) • Change in Nine-Hole-Peg Test (9-HPT) score from baseline to week 48, 96 (and 240) • Change in Timed 25 Foot Walk (T25FW) score from baseline to week 48, 96 (and 240) • Change in the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) score from baseline to week 96 (and 240)
Efficacy Assessments:	MS relapse, Expanded disability scale (EDSS), Magnetic resonance imaging (MRI), Nine Hole Peg Test (9-HPT), Timed 25-foot walk (T25FW), Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

Safety Assessments:	Adverse events, physical examinations, vital signs, laboratory evaluations (blood and urine), pregnancy testing, chest X-ray, concomitant medication, Karnofsky Performance Status
Other Assessments:	Patient related outcomes (PROs), European Quality of Life 5 dimensions (EQ-5D-5L), Multiple Sclerosis Impact Scale (MSIS), Fatigue severity scale (FSS), health economy assessments, immunological/biomarker analyses
Statistical methods:	The primary analysis will use a univariable logistic regression model, conducted as an ITT analysis. Two sensitivity analyses of the ITT analysis will be conducted. First, the analysis above will be repeated in the per protocol population, and secondly, if imbalance in stratification variables in the treatment arms, these covariates will be included in separate multivariable logistic regression models as independent variables to evaluate the influence of these on the results. The secondary efficacy endpoints will be tested in a hierarchal order, to account for multiple comparisons. The secondary endpoints will only be tested and interpreted as confirmatory if the primary efficacy endpoint reach a significance level of 0.05. Subsequent secondary endpoints will only be tested and interpreted as confirmatory if the endpoint listed ahead reaches a significance level of 0.05. Otherwise, the endpoints will be interpreted as non-confirmatory (i.e. descriptive only) independing on the p-values.

FLOW CHART - A

Arm A – HSCT	Screen.	Rand.[1]	Pre-transplantation evaluation, fertility measures	Treatment Period (Mobilization/harvesting, conditioning/ HSCT)		Follow-up period					Follow-up extension period[3]		Unscheduled Visit/ Relapse Visit
						HSCT Day +100	6M	12M	18M (EOS[2])	24M (EOS[2])	30M, 42M, 54M	36M, 48M, 60M/EOXS[2]	-
Visits	V1	V2	V3[4]	V4.1	V4.2	V5	V6	V7	V8	V9	V10, V12, V14	V11, V13, V15	-
Study Week	-12 to -9	-11 to -7	-10 to -4 -6 to -4	0	3 to 6	-	24	48	72	96	120, 168, 216	144, 192, 240	-
Days from treatment start	-84 to -63	-77 to -49	-70 to -28	0	+21 to +42	-	+168 ±7	+336 ±7	+504 ±7	+672 ±7	+X±7	+X±7	-
Days after stem cell reinfusion	-	-	-	-	-	+100 ±3	-	-	-	-	-	-	-
Informed consent [5]	X												
Wash out immunomodulatory treatment[6]		X											
Inclusion/exclusion evaluation	X	X											
Randomization		X											
Pretransplantation check[7]			X										
Fertility conserving measures[8]			X										
Stem cell mobilization and harvesting[9]				X									
Conditioning and autologous HSCT[10]					X								

Arm A – HSCT	**Screen.**	**Rand.[1]**	**Pre-transplantation evaluation, fertility measures**	**Treatment Period (Mobilization/harvesting, conditioning/ HSCT)**		**Follow-up period**					**Follow-up extension period[3]**		**Unscheduled Visit/ Relapse Visit**
						HSCT Day +100	**6M**	**12M**	**18M (EOS[2])**	**24M (EOS[2])**	**30M, 42M, 54M**	**36M, 48M, 60M/EOXS[2]**	**-**
Visits	**V1**	**V2**	**V3[4]**	**V4.1**	**V4.2**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10, V12, V14**	**V11, V13, V15**	**-**
Study Week	**-12 to -9**	**-11 to -7**	**-10 to -4 -6 to -4**	**0**	**3 to 6**	**-**	**24**	**48**	**72**	**96**	**120, 168, 216**	**144, 192, 240**	**-**
Days from treatment start	**-84 to -63**	**-77 to -49**	**-70 to -28**	**0**	**+21 to +42**	**-**	**+168 ±7**	**+336 ±7**	**+504 ±7**	**+672 ±7**	**+X±7**	**+X±7**	**-**
Days after stem cell reinfusion	**-**	**-**	**-**	**-**	**-**	**+100 ±3**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Hematological follow-up						X		X		X		X	
Baseline data (Demographics[11], medical history, MS disease history)	X												
PRO questionnaires[12]				X						X		X	
9-HPT[13], T25FW, BICAMS				X						X		X	
Physical Examination[14]	X		X	X	X	X	X	X	X	X	X	X	X
Chest X-ray	X												
Eccocardiography			X										
Spirometry with DLCO			X										
Oral/dental status[15]			X										

Arm A – HSCT	**Screen.**	**Rand.[1]**	**Pre-transplantation evaluation, fertility measures**	**Treatment Period (Mobilization/harvesting, conditioning/ HSCT)**		**Follow-up period**					**Follow-up extension period[3]**		**Unscheduled Visit/ Relapse Visit**
						HSCT Day +100	**6M**	**12M**	**18M (EOS[2])**	**24M (EOS[2])**	**30M, 42M, 54M**	**36M, 48M, 60M/EOXS[2]**	**-**
Visits	**V1**	**V2**	**V3[4]**	**V4.1**	**V4.2**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10, V12, V14**	**V11, V13, V15**	**-**
Study Week	**-12 to -9**	**-11 to -7**	**-10 to -4 -6 to -4**	**0**	**3 to 6**	**-**	**24**	**48**	**72**	**96**	**120, 168, 216**	**144, 192, 240**	**-**
Days from treatment start	**-84 to -63**	**-77 to -49**	**-70 to -28**	**0**	**+21 to +42**	**-**	**+168 ±7**	**+336 ±7**	**+504 ±7**	**+672 ±7**	**+X±7**	**+X±7**	**-**
Days after stem cell reinfusion	**-**	**-**	**-**	**-**	**-**	**+100 ±3**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Karnofsky[16]				X		X		X		X		X	
Neurology examination (including EDSS) [17]	X			X			X	X	X	X	X	X	X
MRI[18]				X [18]			X	X		X		X[18]	X
MS relapse[19]			X	X	X	X	X	X	X	X	X	X	X
Safety laboratory (blood, urine) [20,21]	X		X	X	X	X	X	X	X	X	X	X	X
Blood Thyroid status	X[22]		X			X	X	X	X	X	X	X	X
Blood Serology [23]	X				X	X							
Pregnancy test [24]	X			X	X	X	X	X					

Arm A – HSCT	**Screen.**	**Rand.[1]**	**Pre-transplantation evaluation, fertility measures**	**Treatment Period (Mobilization/harvesting, conditioning/ HSCT)**		**Follow-up period**					**Follow-up extension period[3]**		**Unscheduled Visit/ Relapse Visit**
						HSCT Day +100	**6M**	**12M**	**18M (EOS[2])**	**24M (EOS[2])**	**30M, 42M, 54M**	**36M, 48M, 60M/EOXS[2]**	**-**
Visits	**V1**	**V2**	**V3[4]**	**V4.1**	**V4.2**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10, V12, V14**	**V11, V13, V15**	**-**
Study Week	**-12 to -9**	**-11 to -7**	**-10 to -4 -6 to -4**	**0**	**3 to 6**	**-**	**24**	**48**	**72**	**96**	**120, 168, 216**	**144, 192, 240**	**-**
Days from treatment start	**-84 to -63**	**-77 to -49**	**-70 to -28**	**0**	**+21 to +42**	**-**	**+168 ±7**	**+336 ±7**	**+504 ±7**	**+672 ±7**	**+X±7**	**+X±7**	**-**
Days after stem cell reinfusion	**-**	**-**	**-**	**-**	**-**	**+100 ±3**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Sampling for biobank and research:													
Whole blood[26,30]	X[32]		X[32]	X	X	X	X	X	X	X	X	X	
Serum[26]	X[32]			X	X	X	X	X	X	X	X	X	
Plasma[26]	X[32]			X	X	X	X	X	X	X	X	X	
DNA (optional)[25,26,29]				X									
Fertility related hormone status(optional) [25,27,31]	X						X	X	X	X		X	
Stool (optional) [25,26,28,31]				X						X		X[28]	
Cerebrospinal fluid (optional)[25,26,28]				X		X		X		X		X[28]	
Transvaginal ultrasound of ovaries (optional)[25,31,32]			X					X		X			
Sperm sampling (optional)[25,31,32]			X				X	X		X			
Stem cell product[32]				X									
Adverse event	X		X	X	X	X	X	X	X	X	X	X	X

Arm A – HSCT	**Screen.**	**Rand.[1]**	**Pre-transplantation evaluation, fertility measures**	**Treatment Period (Mobilization/harvesting, conditioning/ HSCT)**		**Follow-up period**					**Follow-up extension period[3]**		**Unscheduled Visit/ Relapse Visit**
						HSCT Day +100	**6M**	**12M**	**18M (EOS[2])**	**24M (EOS[2])**	**30M, 42M, 54M**	**36M, 48M, 60M/EOXS[2]**	**-**
Visits	**V1**	**V2**	**V3[4]**	**V4.1**	**V4.2**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10, V12, V14**	**V11, V13, V15**	**-**
Study Week	**-12 to -9**	**-11 to -7**	**-10 to -4 -6 to -4**	**0**	**3 to 6**	**-**	**24**	**48**	**72**	**96**	**120, 168, 216**	**144, 192, 240**	**-**
Days from treatment start	**-84 to -63**	**-77 to -49**	**-70 to -28**	**0**	**+21 to +42**	**-**	**+168 ±7**	**+336 ±7**	**+504 ±7**	**+672 ±7**	**+X±7**	**+X±7**	**-**
Days after stem cell reinfusion	**-**	**-**	**-**	**-**	**-**	**+100 ±3**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X
Compliance/drug accountability				X	X								

1. Randomization visit can be performed as a phone visit by study investigator or delegated study personnell to inform the patient about what treatment group he/she is randomized to, and to confirm no relevant changes in patient status since the screening visit.
2. End of study visit (EOS) for patients who prematurely discontinues, preferably all, but as a minimum the following procedures should be performed; hematology, clinical chemistry, liver function parameters, pregnancy test.
3. Depending on future funding of the study extension.
4. Time point for Visit 3 in the HSCT arm will be -10 to -4 weeks before Visit 4.1 depending on fertility conserving measures performed before treatment or not.
5. Visit 1 should be performed within 30 days of signing the informed consent form.
6. Initiate wash out of immunomodulatory treatments according to Table 5.1 in section 5.1.
7. In-depth interview of the patient to collect any additional information to medical history relevant for HSCT, to evaluate the patient's ability to endure the HSCT with regards to both physical and mental health. In addition to blood sampling, this includes lung functions test (spirometry incl. DLCO), echo cardiography, dental examination. Refer to section 6.1.3 for details, and Appendix A for an overview of the plan/logistics.
8. For men and female patients who have accepted to receive fertility conserving measures. Procedures according to national guidelines: For male patients – collection of sperm for storage av Visit 3 only. For female patients - start of hormone therapy for fertility conserving measures and return to clinic for collection of additional samples day 2-5 in menstruation cycle. Harvesting for storage 2-4 weeks later.
9. Harvesting of stem cells takes place10 days after the mobilization.
10. Start of conditioning = "study week 0" and "study day 0". The reinfusion will take place 1 week later and is considered as "HSCT Day 0".
11. Demographics to be collected in this study are gender, year of birth, race and ethnicity.

12. PROs include EQ-5D-5L, FSS and MSIS–29. Additional questionnaires regarding health conditions, work and social status will only be completed by Norwegian patients.
13. To eliminate training effect, the tests should at Visit 4.1 be performed three times in a row. All recordings must be documented in the source documents, and results from the last recording is to be entered in the eCRF.
14. Full clinical examination by physician including; skin (colour, rash, lesions, oedema), lymph nodes, blood pressures, heart rate, body temperature, body height/weight, oral inspection, lung/heart/abdominal examination, peripheral pulse.
15. Dental/oral investigation by dentist/oral or maxillofacial surgeon to identify, prevent or eradicate potenicially infectious foci before the HSCT-associated neutropenic phase
16. Karnofsky performance status score must be entered in source documents and uploaded in the EBMT registry.
17. EDSS should be performed by the same person throughout the study, trained/certified in EDSS scoring.
18. Visit 4.1 MRI should be performed preferably 1-2 days before start of treatment, using the same MRI-machine and administered preferably by the same person per patient during the course of the study. The study specific MRI-protocol is available in the ISF and must be followed. During an extended follow-up periode, MRI will be performed only in week 240.
19. If MS relapse is suspected an unscheduled visits must be performed as soon as possible and preferably within 7 days of onset of symptoms.
20. Hematology; HgB, WBC with differentials, thrombocytes. Liver parameters; ALAT, ASAT, ALP, GT and bilirubin. Clinical chemistry; CRP, creatinine, sodium, potassium, calcium, magnesium, albumin. During Hospital Stay III (conditioning, reinfusion and isolation periode) daily blood sampling for routine clinical monitoring is required (ref. section 6.1.4)
21. Urine strip analysis
22. s-TSH and s-fT4. If abnormal thyroid status at screening (Visit 1) the patient should be excluded from study participation.
23. Serology at screening visit; Quantiferone, hepatitis Bs-virus ag, hepatitis Bs-virus ag and ab, hepatitis Bc-virus ag, EBV ab, CMV ab, hepatitis C virus ab (and hepatitis C PCR when indicated), HIV ab, HTVL ab, toxoplasmosis ab, herpes simplex virus IgM/IgG, varicella zoster virus IgM/IgG. EBV and CMV should be checked weekly from HSCT Day 0 until HSCT Day +100.
24. For female patients of childbearing potential, monthly serum human chorionic gonadotropin (hCG) pregnancy test from start of conditioning until 12 months after last dose of cyclophosphamide.
25. Optional. Separate informed consent must be signed.
26. Samples will be collected for long term storage in Biobank Haukeland, HUS.
27. Required for both male and female patients in both study arms. Fertility related hormones for female patients includes; LH, FSH, AMH, SHBG and E2 estradiol, and for male patients; LH, FSH, SHBG and testosterone.
28. Only to be drawn at 5 year visit during study extension period.
29. DNA biobankning requires only one blood sample to be taken, preferably at Visit 4.1. However, collection at later visits is permitted as long as the informed consent for biobanking remains valid.
30. Whole blood for collection of cells for PBMC and for fixed cells from whole blood (and the stem cell product from patients treated at HUS). PBMC will be done at selected sites only. Fixed whole blood should be collected at all sites and shipped to Sponsor for storage in the biobank. Details are specified in the Laboratory protocol.
31. Applicable only for sites in Norway.
32. Applicable only for Haukeland University Hospital.

FLOW CHART - B

Arm B - Alemtuzumab	Screen.	Rand.[1]	Pre-transpl. evaluation, fertility measures	Treatment Period					Follow-up period		Follow-up extension period[3]		Unscheduled Visit/ Relapse Visit
				Treatment course 1, 0M	-	4M	6M	Treatment course 2, 12M	18M	24M/ EOS[2]	30M, 42M, 54M	36M , 48M, 60M/EOXS[2]	
Visits	**V1**	**V2**	**V3**	**V4.1**	**V4.2**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10, V12, V14**	**V11, V13, V15**	
Study Week	**-3 to -1**	**-2 to 0**	**-**	**0**	**-**	**-**	**24**	**48**	**72**	**96**	**120, 168, 216**	**144, 192, 240**	
Days from treatment start	**-21 to -7**	**-14 to -1**	**-**	**0**	**-**	**+121 ±7**	**+168 ±7**	**+336 ±7**	**+504 ±7**	**+672 ±7**	**+X ±7**	**+X ±7**	
Informed consent[4]	X		-		-								
Wash out immunomodulatory treatment[5]		X	-		-								
Inclusion/exclusion evaluation	X	X	-		-								
Randomization		X	-		-								
Baseline data (Demographics[6], medical history, MS disease history)	X		-		-								
PRO questionnaires[7]			-	X	-					X		X	
9-HPT[8], T25FW, BICAMS				X						X		X	
Physical Examination[9]	X		-	X	-	X	X	X	X	X	X	X	X
Neurology examination[10] (including EDSS)	X		-	X	-		X	X	X	X	X	X	X

Arm B - Alemtuzumab	**Screen.**	**Rand.[1]**	**Pre-transpl. evaluation, fertility measures**	**Treatment Period**					**Follow-up period**		**Follow-up extension period[3]**		**Unscheduled Visit/ Relapse Visit**
				Treatment course 1, 0M	**-**	**4M**	**6M**	**Treatment course 2, 12M**	**18M**	**24M/ EOS[2]**	**30M, 42M, 54M**	**36M , 48M, 60M/EOXS[2]**	
Visits	**V1**	**V2**	**V3**	**V4.1**	**V4.2**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10, V12, V14**	**V11, V13, V15**	
Study Week	**-3 to -1**	**-2 to 0**	**-**	**0**	**-**	**-**	**24**	**48**	**72**	**96**	**120, 168, 216**	**144, 192, 240**	
Days from treatment start	**-21 to -7**	**-14 to -1**	**-**	**0**	**-**	**+121 ±7**	**+168 ±7**	**+336 ±7**	**+504 ±7**	**+672 ±7**	**+X ±7**	**+X ±7**	
Chest X-ray	X		-		-								
MRI [11]			-	X[9]	-		X	X		X		X	X
MS relapse[12]			-	X	-	X	X	X	X	X	X	X	X
Adverse event	X	X	-	X	-		X	X	X	X	X	X	X
Concomitant medication		X	-	X	-		X	X	X	X		X	X
Safety laboratory (blood, urine)[12,13]	X		-	X	-	X	X	X	X	X	X	X	X
Blood Thyroid status[14]	X[14]		-	X	-	X	X	X		X		X	X
Blood Serology[15]	X		-		-								
Pregnancy test[16]	X		-	X	-	X	X	X					
Sampling for biobank and research													
Whole blood[17]	X[25]			X		X	X	X	X	X	X	X	

Arm B - Alemtuzumab	Screen.	Rand.[1]	Pre-transpl. evaluation, fertility measures	Treatment Period					Follow-up period		Follow-up extension period[3]		Unscheduled Visit/ Relapse Visit
				Treatment course 1, 0M	-	4M	6M	Treatment course 2, 12M	18M	24M/ EOS[2]	30M, 42M, 54M	36M , 48M, 60M/EOXS[2]	
Visits	**V1**	**V2**	**V3**	**V4.1**	**V4.2**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10, V12, V14**	**V11, V13, V15**	
Study Week	**-3 to -1**	**-2 to 0**	**-**	**0**	**-**	**-**	**24**	**48**	**72**	**96**	**120, 168, 216**	**144, 192, 240**	
Days from treatment start	**-21 to -7**	**-14 to -1**	**-**	**0**	**-**	**+121 ±7**	**+168 ±7**	**+336 ±7**	**+504 ±7**	**+672 ±7**	**+X ±7**	**+X ±7**	
Serum	X[25]			X		X	X	X	X	X	X	X	
Plasma	X[25]			X		X	X	X	X	X	X	X	
DNA (optional)[18,19,21]				X									
Fertility related hormone status (optional)[18,20,24]	X		-		-		X	X	X	X		X	
Stool (optional)[18,21]				X	-					X		X	
Cerebrospinal fluid (optional)[18,21,22]			-	X	-	X		X		X		X [21]	
Compliance/drug accountability				X	-			X					
Alemtuzumab administration [23]			-	X	-			X					

1. Can be performed as a phone visit by neurologist to inform the patient about what treatment group he/she is randomized to, and to confirm no relevant changes in patient status since the screening visit.
2. End of study visit (EOS) – for patients who prematurely discontinues, preferably all, but as a minimum the following procedures should be performed; hematology, clinical chemistry, liver function parameters, pregnancy test.

3. Depending on future funding of the study extension.
4. Visit 1 should be performed within 30 days of signing the informed consent form.
5. Initiate wash out of immunomodulatory treatments according to Table 5.1 in section 5.1.
6. Demographics to be collected in this study are gender, year of birth, race and ethnicity.
7. PROs include EQ-5D-5L, FSS and MSIS–29. Additional questionnaires regarding health conditions, work and social status will only be completed by norwegian patients.
8. To eliminate training effect, 9-HPT should at Visit 1 be performed three times in a row. All recordings must be documented in the source documents, and results from the last recording is to be entered in the eCRF.
9. Full clinical examination by physician including; skin (colour, rash, lesions, oedema), lymph nodes, blood pressures, heart rate, body temperature, body height/weight, oral inspection, lung/heart/abdominal examination, peripheral pulse.
10. EDSS must be performed by the same person throughout the study, trained/certified within the trial.
11. Visit 4.1 MRI should be performed preferably 1-2 days before start of treatment, using the same machine and administered by the same person per patient during the course of the study. The study specific MRI-protocol is available in the ISF and must be followed. During an extended follow-up periode, MRI will be performed only in week 240.
12. If MS relapse is suspected an unscheduled visits must be performed as soon as possible and preferably within 7 days of onset of symptoms.
13. Hematology; HgB, WBC with differentials, thrombocytes. Liver parameters; ALAT, ASAT, ALP, GT and bilirubin. Clinical chemistry; CRP, creatinine, sodium, potassium, calcium, magnesium, albumin. Urine strip analysis.
14. s-TSH and s-fT4. If abnormal thyroid status at screening (visit 1) the patient should be excluded from study participation.
15. Serology; Quantiferone, hepatitis Bs-virus ag, hepatitis Bs-virus ab, hepatitis Bc-virus Ig, hepatitis C virus ab (and hepatitis C PCR when indicated), HIV ag/ab, HTV types 1 and 2 ag/ab, toxoplasmosis IgM/IgG, herpes simplex virus IgM/IgG, varicella zoster virus IgM/IgG
16. For female patients of childbearing potential, serum human chorionic gonadotropin (hCG) pregnancy test monthly until 4 months after last administration of alemtuzumab.
17. Blood sampling for collection of cells for PBMC and for fixed whole blood. PBMC will be done at selected sites only. Fixed whole blood should be collected at all sites and shipped to Sponsor for storage in the biobank. Details are specified in the Laboratory protocol.
18. Optional. Separate informed consent must be signed.
19. DNA biobankning requires only one blood sample to be taken, preferably at Visit 4.1. However, collection at later visits is permitted as long as the informed consent for biobanking remains valid.
20. Fertility related hormones includes for female patients; LH, FSH, AMH, SHBG and E2 estradiol, and for male patients; LH, FSH, SHBG and testosterone.
21. Sample will be collected for long term storage in the Biobank Haukeland, HUS.
22. CSF only to be drawn at 5 year visit during study extension period.
23. Administration according to current guidelines: at Visit 4.1 (Treatment day “0”) a 5 day cure, at Visit 7 (1 year) a 3 day cure.
24. Applicable only for sites in Norway.
25. Applicable only for Haukeland University Hospital.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
9-HPT	Nine Hole Peg Test
ACTH	Adrenocorticotropic hormone
AE	Adverse Event
ALAT	Alanine transaminase
ALP	Alkaline phosphatase
ARR	Annualized rate of protocol-defined relapses
ASAT	Aspartate transaminase
ASCO	American Society of Clinical Oncology
ATG	Anti-thymocyte globulin
BEAM	Chemotherapy regimen consisting of carmustine, cytarabine, etoposide and melphalan.
BICAMS	The Brief International Cognitive Assessment for Multiple Sclerosis
BMI	Body mass index
BP	Blood pressure
CMSC	Consortium of Multiple Sclerosis Centers
CNS	Central Nervous System
CDI	Confirmed Disability Improvement
CDP	Confirmed Disability Progression
CI	Coordinating Investigator
CMV	Cytomegalovirus
CRP	C-reactive protein
CSA	Clinical Study Agreement
CSF	Cerebrospinal fluid
DAE	Discontinuation due to Adverse Event
DLCO	Diffusing capacity of the lungs for carbon monoxide
DSMB	Data Safety Monitoring Board
EBMT	The European Society for Blood and Marrow Transplantation
EBV	Epstein-Barr virus
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
ELISA	Enzyme-linked immunosorbent assay

EMA	European Medicines Agency
EOS	End of study
EOSX	End of study extension
EQ-5D-5L	EuroQoL 5 dimensions, 5 levels
FEV	Forced expiratory volume
FVC	Forced Vital Capacity
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Gd	Gadolinium
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HSCT	Hematopoietic stem cell transplantation
HSV	Herpes simplex virus
HTLV	Human T-lymphotropic virus type 1 and 2
HUS	Haukeland University Hospital
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product (includes active comparator)
ISF	Investigator Site File
ITT	Intention To Treat
iv	Intra-venous
LVEF	Left ventricular Ejection Fraction
MR	Magneitc resonance
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
MSFC	Multiple sclerosis functional composite
MSIS	Multiple Sclerosis Impact Scale - 29
NEDA	No evidence of disease activity
NorCRIN	Norwegian Clinical Research Infrastructures Network
NYHA	New York Heart Association functional class
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction

PIS	Patient Information Sheet
PG	Project Group
PO	Per oral
PRO	Patient reported outcomes
PPV	Positive predictive value
RRMS	Relapsing remitting multiple sclerosis
SAE	Serious Adverse Event
SC	Steering Committee
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPMS	Secondary progressive multiple sclerosis
T_1	Spin-lattice relaxation time
T_2	Spin-spin relaxation time
T25-FW	Timed-25-Foot Walk
TCR	T-cell receptor
TMF	Trial Master File
TRM	Treatment related mortality
TSH	Thyroid stimulating hormone
VZV	Variicella zoster virus
WBC	White blood cell
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Background – Multiple sclerosis (MS)

MS is a chronic inflammatory disease of the brain and spinal cord. It is most frequently diagnosed at 20-40 years of age. In Scandinavia, the prevalence of MS is approximately 200/100 000[6]. There is no curative treatment. At disease onset, the majority of MS-patients (85 %) have a relapsing remitting disease course (RRMS) with exacerbations followed by complete or partial clinical recoveries.

Relapsing-remitting MS is treated with immunomodulatory medications to prevent relapses and to delay disability development. Immunomodulatory treatment reduces the annually MS relapse rate in RRMS 20-70 %, and recent studies indicate a slower progression of disability compared to studies prior to the era of immunomodulatory MS-treatment[7, 8]. A major proportion of RRMS patients experience disease activity despite the use of registered immunomodulatory MS-treatment, and these patients have significant risk of developing severe disability at a young age[9, 10]. Accordingly, there is a need for improved immunomodulatory treatment options that rapidly and consistently prevent CNS inflammation, MS-relapses and progression of clinical disabilities.

1.2 Background - Therapeutic Information

Every occurrence of inflammatory MS-disease activity has long-term clinical consequences [11, 12]. Pre-relapse function is not regained in more than 30% of MS-relapses[13]. The number/volume of MS-lesions is correlated to long-term disability and to reaching the chronic progressive disease stage[11]. An emerging endpoint is thus the proportion of patients achieving "no evidence of disease activity" (NEDA). NEDA has been defined as no new T_2 lesions or T_1 gadolinium (Gd) enhancing lesions on MRI, no clinical relapses, and no disability progression[2, 14]. In a longitudinal MS cohort the positive predictive value (PPV) of NEDA at 2 years for progression of disability at 7 years was 78 %[14]. The PPV of NEDA at 2 years was greater than each individual component. In the placebo groups of immunomodulatory RRMS treatment studies approximately 7-16 % of patients have NEDA after 2 years[14]. In a cohort study of patients with a disease duration of 5 years or less, only 12% had NEDA after 5 years, and 6 % had NEDA at 7 years[14] In a meta-analysis of immunomodulatory treatment effects in RRMS, the highest ranking immunomodulatory drug for reduction of annualized relapse rate and 3 month confirmed disability progression was alemtuzumab[15]. In a randomized treatment study the proportion of patients treated with alemtuzumab with NEDA over 2 years was 32 % [3].

1.3 Clinical Experience with autologous hematopoietic stem cell transplantation (HSCT)

1.3.1 Treatment effect of autologous HSCT in MS

Data from recently published patient series indicate that autologous hematopoietic stem cell transplantation (HSCT) may have a significantly higher treatment effect than standard RRMS immunomodulatory treatment[16-18]. The premise of autologous hematopoietic stem cell transplantation (HSCT) in MS is that the self-reactive immune response is eradicated by the conditioning regime, and that the immune system is "reset" after reinfusion of autologous hematopoietic stem cells, producing an immune system that is less self-reactive. Early HSCT– studies were mainly small patient series or cohort studies on MS patients with predominantly progressive disease and advanced disability[19]. A large percentage of patients in these studies experienced continued disability progression, consistent with a significant role of neurodegenerative mechanisms at this late disease stage[20]. In more recent non-randomized treatment studies, a major proportion of the study population are RRMS patients with short disease durations and clinically/radiologically highly active inflammatory activity. The study results indicate that HSCT may be an effective treatment option in the RRMS patient group[17, 18, 21, 22]. After HSCT, the inflammatory disease process is halted for several years in a majority of MS patients. In a study of 145 MS

patients (81 % RRMS, 19 % SPMS) treated with HSCT, using low intensity conditioning based on Cyclophosphamide, 80 % of patients had NEDA over 2 years, and 68 % had NEDA over 4 years after treatment[17]. In a patient series of 41 MS patients (34 patients with RRMS) treated with medium or high intensity conditioning HSCT in a multicentre study in Sweden, 68 % had NEDA over 5 years[18]. In an interim analysis of an ongoing, multicentre, single-arm clinical trial of HSCT for RRMS patients who experienced treatment failure on other immunomodulatory treatment, 24 patients received HSCT. The study participants received medium intensity conditioning with carmustine, etoposide, cytarabine, and melphalan (BEAM). 78.4% of the treated patients had NEDA at 3 years[22]. In a recent single-group phase 2 trial at three hospitals in Canada 24 patients (50 % RRMS, 50 % SPMS) received high intensity myeloablative conditioning with busulfan, cyclophosphamide, and rabbit anti-thymocyte globulin, followed by autologous HSCT[21]. 70% of patients had no disease activity (NEDA) at 3 years after transplantation. The patients had no MS relapses, new Gd-enhancing lesions or new T_2 lesions during a median follow-up of 6.7 years. The yearly rate of brain atrophy decreased to a level comparable with healthy controls. These results are not directly comparable to data from randomized and controlled studies with registered immunomodulatory treatments due to differences in patient populations and study designs. A significant proportion of patients in several of the HSCT studies had progressive MS or did not meet the inclusion criteria, or the inclusion criteria were significantly different than criteria used in randomized trials of immunomodulatory MS treatment. The autologous HSCT-studies were not randomized, and did not include a control group. The proportion of patients with NEDA may also vary depending on the clinical and radiological pre– and post-treatment follow-up protocols.

1.3.2 Side effects of autologous HSCT

There is a risk for serious side effects of HSCT, mainly due to the toxicity of the conditioning regimens. The HSCTrelated mortality rate reported to The European Society for Blood and Marrow Transplantation (EBMT) from 1995 to 2000 was 7.3 %, whereas from 2001 to 2007 it was significantly lower; 1.3 %. This change may be due to better patient selection and improved investigator experience, but could also be associated with a concomitant switch from high intensity conditioning to the use of medium intensity (BEAM) or low intensity, cyclophosphamide-based conditioning regimens. In the 4 most recently reported MS patient series of non-myeloablative conditioning 299 patients were treated, and there was no registered treatment related death[17, 18, 22, 23]. In a recently reported MS patient material treated with a high intensity myeloablative conditioning regimen, consisting of busulfan, cyclophosphamide and anti-thymocyte globulin (ATG), one of the 24 patients died of transplantation-related complications[21]. Other frequent serious side effects of HSCT include, neutropenic fever, infectious diseases complicated with bacteremia/sepsis, hemorrhagic cystitis, liver toxicity and reactivation of varicella virus Epstein-Barr virus (EBV) or cytomegalovirus (CMV).. Mucositis and diarrhea were more prevalent in early studies using medium and high intensity conditioning regimens. Following the immediate post transplant period (which per definition extends to HSCT day +100), there is an increased risk of secondary autoimmune diseases, including thyroid disease and immunological thrombocytopenia (ITP). The incidence rate of autoimmunity has been reported to be lower in treatment protocols using ATG than in protocols including alemtuzumab[17], and also lower than registered when treating with alemtuzumab alone[16].

1.3.3 Autologous HSCT: Mechanisms of action

In autoimmune diseases like MS, autologous HSCT is applied to eradicate the autoimmune immunological memory and to regenerate a naïve and self-tolerant immune system from hematopoietic precursors[24] . However, the mechanisms of action of HSCT in MS patients still need to be clarified. The MS-disease process is believed to be driven by the adaptive immune system, comprising T cells and B cells. One hypothesis is that HSCT works by eradicating autoreactive T cells and B cells, replacing them with a non-autoimmune repertoire. One study using high-throughput sequencing of T cell receptor (TCR) beta-chains following HSCT showed that the CD4+ T cell repertoire was replaced to a larger extent than the CD8+ T cell repertoire[25]. The B cell repertoire has so far not been investigated in HSCT. Another study has demonstrated that HSCT promotes anti-inflammatory T cell responses[17]. Distinct cytokine profiles may be associated with high MS activity and flares[26]. As recommended by the EBMT, a wide array of immunological parameters should thus be monitored in prospective HSCT-studies in MS[27].

1.3.4 Autologous HSCT: Markers of treatment response

It is known from Systematic follow-up studies demonstrate that in 20-30 % of the patients new disease activity is observed 2-5 years after HSCT [17, 18]. It is, however, not known why some patients relapse after treatment whereas others seem to respond very well. It has been shown that a less diverse post-treatment TCR repertoire is associated with a poor response [25]. Thus, pre- and post-treatment characterization of the TCR and probably also the B cell receptor (BCR) repertoires, and post-treatment monitoring of possible pathogenic T and B cell clones may provide important clues to why the treatment fails in a subgroup of MS patients. Finally, it will be of interest to investigate whether the oligoclonal B cell response in the cerebrospinal fluid, which is a hallmark of the disease, remains after successful treatment with HSCT [28]. Detection of other immunological biomarkers and pre- and post transplant cytokine levels may also be of value in reflecting treatment responses after HSCT in RRMS patients[27].

1.4 Rationale and purpose for the study

This study is a randomized multicentre treatment study of RRMS patients with breakthrough inflammatory disease activity in spite of ongoing standard immunomodulatory medication. The study has two treatment arms; arm A: HSCT and arm B: alemtuzumab, a registered immunomodulatory treatment of RRMS. A pre-planned 3-year follow-up extension period will be performed depending on future funding.

The aim of the study is to assess the effectiveness and side effects of a new treatment intervention in RRMS; HSCT, and, thereby, the value of HSCT in clinical practice. Data from recently published patient series indicate that HSCT may have a significantly higher treatment effect than currently registered RRMS immunomodulatory treatments[16-18]. This study will determine the relative role of HSCT versus alemtuzumab.

The main hypothesis of the study:

HSCT is superior to EMA–approved immunomodulatory drugs in preventing further inflammatory disease activity and/or development of disability in RRMS patients with recent breakthrough inflammatory disease activity.

This is a randomized study of autologous HSCT using a low intensity, non-ablative conditioning regimen with cyclophosphamide and ATG versus treatment with the currently presumed best available immunomodulatory medication (alemtuzumab) in RRMS patients with significant inflammatory disease activity in spite of ongoing immunomodulatory MS treatment. Significant disease activity is defined as having one or more clinically reported multiple sclerosis (MS) relapse(s), AND 1 or more T_1 Gd-enhanced lesion(s), OR three or more new or enlarging T_2 lesions on magnetic resonance imaging (MRI) over the last year while being treated on immunomodulatory medication by standard national guidelines. The relapse(s) must have occurred 3 or more months after the onset of an immunomodulatory treatment, asimmunomodulatory treatment in MS may reach full effect after 3 months or more[2].

Both the knowledge of the treatment effect of registered immunomodulatory therapies for RRMS, and the number of treatments approved for RRMS by the European Medicines Agency (EMA) are rapidly increasing. During the study period, there may thus appear new supplementing information on other MS immunomodulatory treatments that favour the use of a new comparator (replacing or supplementing alemtuzumab as a comparator). This will be evaluated by the PMC if applicable during the study period and the planned extension period.

If the treatment efficacy obtained by HSCT is better than the currently most efficacious standard,immunomodulatory treatment in randomized treatment trials, HSCT will likely be approved as a part of the standard treatment recommendations for a significant proportion of RRMS patients. A randomized study regarding the clinical outcome of autologous HSCT compared to a standard immunomodulatory treatment in MS has not yet been published. Except for Sweden, HSCT is currently not registered as a part of standard MS treatment in the public health services of Europe.The HSCT regimen for the study will be identical to the regimen used in similar patient populations in Sweden, Norway and the USA[17, 18].

Alemtuzumab has been chosen as the primary comparator, because it is the immunomodulatory medication currently authorised by the EMA for treatment of RRMS with the most favourable therapeutic effects. In a meta-analysis of immunomodulatory treatment effects in RRMS, alemtuzumab was the immunomodulatory drug with the most eminent reduction of annualized relapse rate and 3 month confirmed disability progression [15].

In this study, a health economic evaluation will be included. Accordingly, the proposed study should provide a robust basis for future official decisions regarding the role of HSCT in RRMS treatment.

1.5 Benefit-risk assessment

The risk to subjects in this trial will be minimized by compliance with eligibility criteria, close clinical monitoring, avoidance of prohibited treatments and adherence to protocol contraception requirements and Investigator guidance regarding specific safety areas. The inclusion of an active comparator arm ensures that all patients in the study will receive active therapy.

The overall benefits and safety profile for autologous HSCT has been outlined in section 1.3.

Data suggest that the treatment related mortality with HSCT can be decreased to 1–2 % in experienced centres using HSCT with mainly conditioning of high and medium intensities, and it has been even lower (≤ 0.3 %) in MS patients treated with low intensity conditoning regimens[17, 18, 21, 29-31]. However, the mortality rate for HSCT has not been compared to that of other immunomodulatory MS treatments in a prospective randomized clinical study.

MS is associated with an extensive loss of quality-adjusted life years[32, 33] Despite the risk of treatment related mortality and serious side effects, the overall longterm benefits associated with HSCTthus support continued research on HSCT and treatment of RRMS[29, 34].

The comparator alemtuzumab is approved for the treatment of relapsing RRMS. In controlled clinical trials, treatment with alemtuzumab was associated with autoimmune thyroid disorders in 30-40 % of patients, serious events of idiopathic thrombocytopenic purpura in approximately 1 %, and nephropaties, including anti-glomerular basement membrane (anti-GBM) disease in 0.3 % during a 48-53 months follow-up period after an initial LEMTRADA exposure[16]. Treatment with alemtuzumab is associated with an increased risk of infections, including but not restricted to urinary tract infection, upper respiratory tract infection, sinusitis, oral herpes, influenza, and bronchitis. The most common adverse reactions with alemtuzumab (in ≥20% of patients) are rash, headache, pyrexia, and respiratory tract infections. The efficacy of alemtuzumab in reducing clinical (ARR and disability progression) and MRI disease activity as well as brain volume loss, has been demonstrated in Phase 3 clinical trials[3, 35].
Overall, the balance of benefits and risks support a clinical study to evaluate the potential of HSCT as an effective and safe therapy in the target population.

2 STUDY OBJECTIVES AND RELATED ENDPOINTS

2.1 Study objective

The objective of this prospective, randomized study is to investigate the efficacy and safety of HSCT compared to alemtuzumab in patients with aggressive relapsing remitting MS.

In Norway, the clinical study is supplemented with a health economic evaluation.

2.2 Primary endpoint

The primary efficacy endpoint of this prospective, randomized study is to determine differences between patients in the 2 treatment arms according to the following criteria:

- Proportion of patients with no evidence of disease activity (NEDA, as defined per protocol) during a 2 year (96 week) period
- Pre-planned study extension: Proportion of patients with NEDA (as defined per protocol) during a 5 year (240 week) period.

NEDA is the absence of a protocol defined disease activity event.

A protocol-defined disease activity event is the occurrence of at least one of the following:
- A new T_1 Gd-enhanced lesion on MRI of the brain and spinal cord
- A new T_2 hyperintense lesion on MRI of brain and spinal cord
- A protocol-defined MS relapse (see below)
- 24 week confirmed disability progression based on increases in Expanded Disability Status Scale (EDSS) (see below and Appendix C)

MS relapse is defined as new or worsening neurological symptoms attributable to MS, lasting at least 48 hours, without pyrexia, with an objective change on neurological examination after at least 30 days of clinical stability.

Disability progression is defined as an increase of one point in the EDSS score (or half a point if the baseline EDSS score was equal to 5.5), confirmed after 24 weeks, with an absence of relapse at the time of assessment. MRI imaging will be performed according to the Revised Consortium of Multiple Sclerosis Centers (CMSC) MRI Protocol and Guidelines[4]

2.3 Secondary endpoints

The secondary efficacy endpoints for this study are to evaluate the efficacy of the study treatments on the basis of the following endpoints:

- Proportion of patients with no evidence of disease activity, including atrophy (NEDA 4), as per protocol defined disease activity events (as defined in section 2.2) plus atrophy (measured yearly atrophy above threshold of 0, 4 %) during a 2 year (96 week) period[5].
    - Pre-planned study extension: Proportion of patients who have NEDA 4 during a 5 year (240 week) period.
- Time to first protocol-defined disease activity event as defined in section 2.2
- Change in EDSS from baseline (Visit 4.1) to Weeks 96 and 240
- The proportion of patients who, at Week 96, have protocol-defined Confirmed Disability Improvement (CDI) , confirmed stable EDSS or Confirmed Disability Progression (CDP) compared to baseline
- Annualized rate of protocol-defined relapses during 96 weeks
- Time to onset of first protocol-defined relapse
- Change in MRI T_2-weighted hyperintense lesion volume from baseline to Weeks 48 and 96 (and 240)
- Change in MRI T_1-weighted hypointense lesion volume from baseline to Weeks 48 and 96 (and 240)
- Change in brain volume from baseline to week 48 and week 96 (and week 240), and from week 48 to week 96 (and week 240)[5]

- Time to detection of a new MRI T_2 lesion
- Total number of MRI T_1-weighted Gd-enhanced lesions at weeks 24, 48, 96 (and 240)
- Proportion of patients free from T_1 Gd-enhancing lesions at weeks 24, 48, 96 (and 240)
- Change in Nine-hole-peg test (9-HPT) score from baseline to week 48, 96 (and 240)
- Change in Timed 25 foot walk (T25FW) score from baseline to week 48, 96 (and 240)
- Change in The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) score from baseline to week 96 (and 240)

2.4 Exploratory endpoints

- To further assess the efficacy of the study treatments over the study period, the following outcome data, including patient-reported outcomes (PROs) will be obtained at baseline and in week 96 (and 240):
    - EQ-5D-5L
    - Fatigue Severity Scale (FSS)
    - Multiple Sclerosis Impact Scale (MSIS) - 29
    - Severity of relapses (residual disability (EDSS) after relapses)

- To characterise immune repertoires and markers of therapeutic response in blood and in CSF, and in accordance with EBMT recommendations regarding immune monitoring after HSCT in autoimmune diseases[24] and recent findings in MS research, immunological analyses will include at a minimum;
    - Immunocytometric analyses (subsets of major cellular populations)
    - T cell receptor sequencing
    - B cell receptor sequencing
    - Isoelectric focusing
    - ELISA for levels of neurofilament light chain
    - Proteomic study for potential other biomarkers for therapeutic response
    - Detection of cytokine profiles

- Overall survival rate at week 96 (and week 240)
- Work productivity and activity impairment at week 96 (and 240)

2.5 Safety endpoints

The safety objective for this study is to evaluate the tolerability of the study treatments usingthe following endpoints:

- Rate and nature of adverse events
- Frequency of serious adverse events
- Clinical relevant changes in vital signs
- Clinical relevant changes on physical examinations
- Clinical relevant changes in clinical laboratory results.
- Non-MS central nervous system (CNS) pathology
- Use of concomitant medications, including pre-medications and medications used during the study period

3 OVERALL STUDY DESIGN

3.1 Overall study design and plan

This study is a prospective, multicentre, interventional, unblinded, randomized, parallel group study to investigate the efficacy and safety of autologous HSCT compared to the current standard of treatment with alemtuzumab, in patients with relapsing remitting MS experiencing treatment failure in the preceeding year in spite of ongoing immunomodulatory treatment. If a new immunomodulatory MS treatment is registered during the study recruitment phase it will be evaluated if the new treatment should be added as comparator.

The study design is chosen because it is expected to produce results which clarify the relative efficacy of HSCT versus the currently considered most efficient standard immunomodulatory drug used for RRMS. This prospective, randomized study will provide data with impact on the possibility of HSCT to be accepted as a standard immunomodulatory treatment option for RRMS [19].

The target group of this study is RRMS patients with breakthrough inflammatory disease activity while on other immunomodulatory MS treatment. The study will enroll approximately 100 patients. Patients will be assessed for primary and secondary efficacy endpoints and safety parameters following study treatments at predefined timepoints (scheduled study visits) and supplementing, unscheduled study visits, see section 6.1.5.

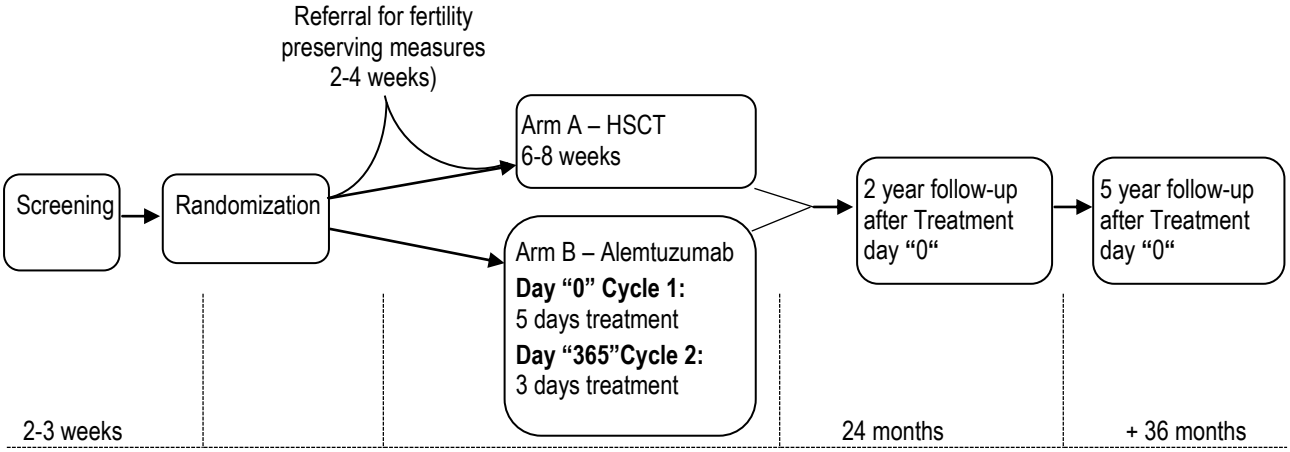

Figure 3.1:1 Study design

Patients are included in the trial once they have signed the informed consent form (ICF). All patients considered suitable after screening and meeting the inclusion criteria and none of the exclusion criteria will be randomized to one of the treatment arms. The randomization will be unblinded.The patients will be assigned at a ratio of 1:1 to either HSCT (arm A) or i the currently most efficient of currently registered immunomodulatory treatment (arm B). The patient assignment is stratified by age, sex and residency (country).

Patient participation is concluded when they have completed the last planned study visit. The end of study is defined as "last patient out" (LPO), i.e. last visit completed by last patient after 2 year follow-up period, and for the planned study extension after 5 year follow-up period. Enrollment of patients into the study is competitive, however, if recruitment on country level exceeds agreed target this must be approved by the Sponsor. Randomization of required number of patients into the study is estimated to take 2 years. The estimated study

duration is expected to be maximum 4 years. If the pre-planned study extension to conduct a 5-years follow-up period receives financial funding, the total study duration will be maximum 7 years.

3.2 Administrative structure of the study

This study is initiated by a team of collaborating physicians at the Department og Neurology, the Medical Department and the Department of Immunology and Transfusion Medicine at the central study site at Haukeland University Hospital (HUS) in Norway in close interaction with national and international PIs, co-PIs and research collaborators. The Sponsor of this study is Helse Bergen HF, Haukeland University Hospital (HUS), and the study will be conducted as a multicentre study in Norway, Sweden, Denmark and possibly other European countries.

The members of a Project Management Committee (PMC) and a Coordinating Investigator (CI) are assigned by the Sponsor. The PMC has the overall responsibility for the planning, conduct and reporting in the study. Use of study data and biological material for additional scientific substudies will be determined by the PMC. The CI is responsible for coordination of clinical investigators at defined study sites. . Medical Officers will be assigned and provide medical counselling to all participating study sites.

Approval by Ethics Committees and Health Authorities must be available as applicable.

An international Reference Group (RG) consisting of independent experts will be established to provide clinical and/or scientific advice for the Sponsor, PMC and CI. The composition, tasks and responisibilities of the RG will be documented in the Trial Master File (TMF).

The organization of the study at participating sites will be done according to agreed responsibilities and tasks. A signed contract must be filed before the initiation of the clinical study. Tasks and functions assigned in order to organize, manage and evaluate the study will be defined per Norwegian Clinical Research Infrastructures Network (NorCRIN) SOPs. A list of responsible clinicians (specialists in neurology and hematology comprising Principal investigators (PI) and co-PIs) at each study site will be given in the TMF. Any substantial amendments to the study protocol will be discussed and clarified with PIs and co-PIs, and with other research collaborators if applicable. follow-up GCP-training conducted within the last 5 years is compulsory for all members of the PMC, as well as for all PIs and co-PIs. Neurologists performing EDSS-scorings at study visits also need to document recent EDSS certification. The Sponsor can provide formal training and certification in EDSS scoring for all relevant study personnel, see section 7.1.3. Curriculum vitae will be obtained from all formal clinical study personell as well as assigned research collaborators, and all documentation will be filed in the Investigator Site File (ISF).

Data management will be handled by the Clnical Trial Unit at Oslo University Hospital, Norway, who will provide the eCRF and Randomization system. The study will use electronic CRF (eCRF) and randomization from Viedoc™, with role based access control, an interactive eCRF with in-data validation and signing, monitoring/locking functions, internal reporting of AEs and SAEs with notification to the Medical Officer, Monitor and representatives from the PMC as applicable, and data export. Viedoc™ will provide block randomization and will be provided with 50% of patients in each treatment group, stratified for age, sex and country. The SOPs for Department for clinical research support will apply for these services.
The Norwegian Clinical Infrastructures Network (NorCRIN), and NorCRIN's SOPs will be used for planning and execution of study monitoring.
Statistical evaluations will be performed by statistical expertise at HUS.

Defined safety laboratory measurements will be analysed at each study site according to local procedures.. Reference ranges from local laboratories will be provided to the Data Management for programming into the eCRF. The central biobank involved in studyspecific sampling and long-term storage of biological material for future research will be Biobank Haukeland located at HUS. Details regarding biobanking are specified in a separate document available in the ISF and in section 7.4 of the protocol.

A Data Safety Monitoring Board (DSMB) independent of the Sponsor will assess the progress of the trial, including safety and efficacy assessments at specified intervals. The DSMB will advice the Sponsor on whether to continue, modify, or stop the trial. The tasks and responsibilities of the DSMB will be specified in a separate charter filed in the TMF.

A central study radiology reading centre will be appointed by the PMC.

Spinal fluid proteomic analyses will be performed by the Proteomics group at the University of Bergen, Department of Biomedicine. Spinal fluid and blood immunological analyses will be performed at research laboratories at HUS and Akershus University Hospital. Other collaborating research institutes are Sahlgrenska Academy University of Gothenburg,Rigshospitalet Copenhagen, and the VUmc MS Center in Amsterdam.

The users of this study are RRMS patients. Representatives from a national MS patient organization, The Norwegian MS Society (MS-Forbundet),have been included in planning this study. Their representatives will also be involved in the following tages of the study through representation in the RG, and in informing the MS patient population of the study progress,results, and about the implications of study results on the routine medical treatment of RRMS patients. This is to ensure that all aspects of the study are in accordance with the best interest of the target group.

4 STUDY POPULATION

4.1 Selection of study population

An appropriate number of RRMS-patients will be screened in Norway, Sweden, Denmark and possibly other European countries. . National/regional study sites will be assigned to ensure that approximately 100 patients are randomized within the estimated timeframe of 2 years. If enrollment is delayed or the enrollment rate is lower than anticipated, additional sites might be assigned by Sponsor. The number of patients included may be increased during the study period if study drop out or event rates differ from expected levels.

Every patient who fulfils the inclusion criteria and does not fulfil any exclusion criteria will be randomized, and receive the allocated study treatment.

Re-testing:

Re-testing for eligibility criteria is only to be performed once for a laboratory result which is obviously received beyond stability or thought to be a spurious result based on earlier laboratory values for a patient. To avoid protocol violations, a re-test should be carried out as soon as possible to ensure that the result of the laboratory test is received within the next planned visit window.

Re-screening:

Re-screening of a patient is only allowed once. If failing, the patient should be declared as a screening failure in the eCRF with their originally allocated patient number, and a new patient number will be assigned at the time of re-screening. The patient must be re-consented using the currently approved versions of the Patient Information Sheet (PIS) and Informed Consent Form (ICF).

A log of all patients enrolled into the study (i.e. having signed the Informed Consent Form) must be maintained by the site staff in the ISF at the investigational site irrespective of whether they have been treated with an investigational drug or not. This log should clearly identify any re-screened patient.

4.2 Inclusion criteria

All of the following conditions must apply to the prospective patient at screening visit prior to receiving study treatment:

1. Age between ≥18 to ≤50, both genders

2. Women of childbearing potential* (WOCBP) and men in a sexual relation with WOCBP must be ready and able to use highly effective methods of birth control¥ per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly.

3. Diagnosis of RRMS using revised McDonald criteria of clinically definite MS[1]

4. An EDSS score of 0 to 5.5

5. Significant inflammatory disease activity in the last year despite treatment with standard disease modifying therapy (interferon beta, glatiramer acetate, dimethyl fumarate, teriflunomide, fingolimod, natalizumab)

    a. Significant inflammatory disease activity is defined by:

        i. One or more clinically reported multiple sclerosis (MS) relapse(s),

        ii. AND 1 or more T_1 Gd-enhanced lesion(s),

        iii. OR three or more new or enlarging T_2 lesions on magnetic resonance imaging (MRI)

    The relapse(s) must have been treated with iv or oral high dose corticosteroids prescribed by a neurologist, and must have occurred 3 or more months after the onset of an immunomodulatory treatment, as MS immunomodulatory treatment may reach full effect after 3 months or more[2].

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* A woman is considered of childbearing potential (WOCBP) if;
- having experienced menarche and
- not postmenopausal (12 months with no menses without an alternative medical cause) and
- not permanently sterilised (e.g., hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

¥ Highly effective birth control methods are;
- combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation
- progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

6. The patient is a RRMS-patient referred from neurological departments in Norway, Denmark, Sweden or possibly other European countries to an assigned study site.

7. Signed informed consent and expected patient cooperation regarding the treatment schemes and procedures planned in the treatment and follow-up periods must be obtained and documented according to ICH GCP and national/local regulations.

4.3 Exclusion criteria

Patients will be excluded from the study if they meet any of the following criteria at screening visit (V1):

1. Known hypersensitivity or other known serious side effects for any of the study medications, including co-medications such as high-dose glucocorticosteroids

2. Any illness or prior treatment that in the opinion of the investigators would jeopardize the ability of the patient to tolerate aggressive chemotherapy or high-dose glucocorticosteroids

3. Any ongoing infection, including CMV, EBV, HSV, VZV, hepatitis virus, toxoplasmosis, HTV, HIV or syphilis infections, as well as heaptitis B surface antigen positivity and/or hepatitis C PCR positivity verified at Visit 1

4. Patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV), unless tested for antibodies to VZV. VZV negative patients can only be included if they receive vaccination against VZV at least 6 weeks prior to inclusion.

5. Current or previous treatments with long-term effects that may influence the treatment effects or potential toxicities/side effects of the treatment arms. This includes, but is not restricted to previous treatment with rituximab, mitoxantrone, cladribin and alemtuzumab

6. Treatment with glucocorticoids or ACTH within one month prior to study inclusion

7. Having experienced an MS relapse within one month prior to study inclusion

8. Prior or current major depression

9. Prior or current psychiatric illness, mental deficiency or cognitive dysfunction influencing the patient ability to make an informed consent or comply with the treatment and follow-up phases of this protocol.

10. Prior or current alcohol or drug dependencies

11. Cardiac insufficiency, cardiomyopathy, significant cardiac dysrhytmia, unstable or advanced ischemic heart disease (NYHA III or IV)

12. Significant hypertension: BP > 180/110

13. Prior history of malignancy except localized basal cell, squamous skin cancer or carcinoma in situ of the cervix.

14. Known thyroid disease, and/or abnormal serum thyroid hormone status

15. Failure to willingly accept or comprehend risk of irreversible sterility as a side effect of therapy

16. WBC < 1,5 x 10^9/L

17. Platelet (thrombocyte) count < 100 x 10^9/L

18. ALAT and/or ASAT more than 2 times the upper normal reference limit (UNL)

19. Serum creatinine > 200 µmol/L

20. Serum bilirubin > 20 µmol/L

21. Presence of metallic objects implanted in the body that would preclude the ability of the patient to safely have MRI exams

22. Diagnosis of primary progressive MS

23. Diagnosis of secondary progressive MS

24. Treatment with natalizumab, fingolimod and dimetylfumurat within the last 2 months (washout must be performed as specified in section 5.1)

25. Use of teriflunomide (Aubagio®) within the previous 2 years unless cleared from the body (plasma concentration < 0.02mcg/ml following elimination from the body with cholestyramine or activated powdered charcoal) as specified in section 5.1

26. Any hereditary neurological disease such as Charcot-Marie-Tooth disease or Spinocerebellar ataxia

27. Any disease that can influence the patient safety and compliance, or the evaluation of disability

28. History of hypersensitivity reaction to rabbit

29. Women who are pregnant, breast-feeding, or who plan to become pregnant within the timeframe of this study

30. Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s). Patients participating in a purely observational trial will not be excluded.

4.4 Removal of patients from therapy or assessments

4.4.1 Removal of individual patients

This is a long-term study and all patients should be encouraged to stay compliant with the study protocol and remain in the study, if continued study participation is found to be medically safe and in the best interest of the patient.

Permanent study medication discontinuation is only justified when a clear and persistent contraindication arises, or if the patient request to stop study treatment (i.e. not to receive the second treatment cure with alemtuzumab at the 1 year visit (Visit 7)).

An excessive withdrawal rate can severely impact the scientific value of the study. The “Intention to treat” (ITT) analysis requires that all randomized patients be followed until end of study. This includes careful patient selection and appropriate explanation of the study procedures and visit schedule prior to enrolment, including an explanation of the consequences of premature withdrawal.

Withdrawal of informed consent
A patient has the right to withdraw informed consent for participation at any time for any reason. However, withdrawal of consent should be very rare and unusual. Patients must be informed that they can withdraw from the study without withdrawing consent and perhaps agree to the collection of their vital status e.g. by phone. A true withdrawal of consent means that the patient cannot be contacted about the study again. Because of this, the Investigator must be involved in the discussion with the patient regarding a withdrawal of consent, and preferably discuss the withdrawal of consent with the Sponsor’s representative prior to study discontinuation.

If the patient withdraws informed consent for participation in the study, the study will end for the patient. The patient must stop receiving study medication, and should be asked to return to the clinic for the end of study visit and perform assessments as described in the Flow Chart.

Patient lost to follow-up
If a patient is lost to follow-up, every effort should be made by the investigator and site staff to contact and locate the patient before the patient is declared lost to follow-up. Investigators and site staff must use every possible means, according to local regulations, to locate patients who have missed visits.

Pregnancy
If a patient becomes pregnant during the study, the study medication will be stopped, and the patient will be followed according to the patient's original scheduled study visits during the trial, and until birth or termination of the pregnancy. Due to the nature of the disease under study, patients who become pregnant during the course of the study will be removed from per protocol analysis.

4.4.2 Trial Discontinuation

The overall study or a specific study site, or a patient may be discontinued at any time at the discretion of the Sponsor in the event of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration, invalidating the earlier positive benefit-risk-assessment
- Incorrect enrollment, i.e. the patient does not meet the inclusion/exclusion criteria
- Violation of GCP, the clinical study protocol, or the contract, affecting the continued performance of the trial
- Failure to reach required recruitment targets on trial level or at a specific study site

The Sponsor, PMC and CI will inform all investigators, relevant Competent Authorities and Ethics Committees in case of a prescheduled termination of the study along with the reasons for such an action. If the study is terminated early on grounds of safety, the Competent Authorities and Ethics Committees will be informed within 15 days.

5 TREATMENTS

In this study cyclophosphamide, anti-thymocyte globulin and alemtuzumab are defined as Investigational Medicinal Product(s) (IMPs):

Cyclophosphamide (Sendoxan®), powder for iv injection fluid. For storage and preparation instructions see the SmPC.

Anti-thymocyte globuline (Thymoglobuline®), powder for iv infusion fluid. For storage and preparation instructions see the SmPC.

Alemtuzumab (Lemtrada®), concentrate for iv infusion fluid. For storage and preparation instructions see the SmPC.

A schematic illustration of the treatments/patient flows is available in Appendix A.

5.1 Wash-out of immunomodulatory treatment(s)

Patients with RRMS experiencing treatment failure on immunomodulatory treatments the previous year will need to follow the below timelines for wash out before start of study treatment. Wash out should start after eligibility and randomization is confirmed (i.e. at Visit 2).

Tabell 5.1.1 Wash out duration

Treatment	Time until start of study treatment	
	Study arm A:	Study arm B:
Natalizumab	2 months	2 months
Fingolimod	2 months	2 months
Dimetylfumurat	2 months	2 months
Glatiramer acetate	No wash-out required	No wash-out required
Beta interferons	No wash-out required	No wash-out required
Teriflunomide*	After stopping treatment with teriflunomide: • cholestyramine 8 g is administered 3 times daily for a period of 11 days, or cholestyramine 4 g three times a day can be used, if cholestyramine 8 g three times a day is not well tolerated, • alternatively, 50 g of activated powdered charcoal is administered every 12 hours for a period of 11 days.	After stopping treatment with teriflunomide: • cholestyramine 8 g is administered 3 times daily for a period of 11 days, or cholestyramine 4 g three times a day can be used, if cholestyramine 8 g three times a day is not well tolerated, • alternatively, 50 g of activated powdered charcoal is administered every 12 hours for a period of 11 days.

* Accelerated elimination procedure: Teriflunomide is eliminated slowly from the plasma. Without an accelerated elimination procedure, it takes an average of 8 months to reach plasma concentrations less than 0.02 mg/l, although due to individual variation in substance clearance it may take up to 2 years. An accelerated elimination procedure can be used at any time after discontinuation of teriflunomide (see section 4.6 and 5.2 for procedural details).

5.2 Dosage and drug administration (study treatments and supportive care)

The study treatments and supportive care medication will be administered to the subject by authorized site personnel only.

5.2.1 Selection of doses

Cyclophosphamide and anti-thymocyte globulin are approved drugs for treatment of various autoimmune diseases, including eradication of self-reactive immune response by the conditioning regime prior to autologous stem cell transplantation, as described in section 5.2.2. The conditioning regimens used for HSCT in MS can be separated into high, intermediate and low dose intensity. In MS treatment studies using high intensity HSCT regimen treatment related mortality was approximately 4%, while the mortality rate was lower in MS patients treated with low or medium intensity conditioning regimens[17, 18, 21, 29, 30] A recent meta analysis found no significant differences in 2-year rates of disability progression in patients treated with HSCT using high, intermediate and low regimen intensities[34]. The highest proportion of MS-patients with NEDA at 24 months was found in a serie of 145 patients, using HSCT with low regimen intensity[17, 34]. Given these results regarding treament effect and treatment related mortality using high, intermediate and low intensity conditioning regimens, a low intensity regimen has been selected for use in this trial.

Alemtuzumab is an approved treatment of adult patients with relapsing remitting multiple sclerosis, and is considered to be the most effective immunomodulating for treatment of MS. The selected dose is in accordance with literature recommendations and clinical practice.

For more details see the current version of the SmPCs.

5.2.2 STUDY ARM A (HSCT):

Mobilization and peripheral blood stem cell harvesting

Priming chemotherapy (cyclophosphamide) is included in the standard study mobilization regimen to enhance mobilization while maintaining disease control and to prevent a potential flare, which may be a consequence of granulocyte colony stimulating factor therapy alone[36].

Day 1: Cyclophosphamide 2.0 g/m^2 body surface area will be given iv in 1000 ml of standard glucose (glucose 50mg/ml) over 60 minutes. The cyclophosphamide dose is highly emetogenic, and an appropriate, combined antiemetic regime should be used[37-39]. A forced diuresis with a desired minimum volume of 150 ml urine/hour is obtained by infusion of at least 3000 ml of normal saline iv supplemented with 20 ml furosemide/1000 ml fluid, and complementary doses of 20 mg furosemide iv to obtain the required urinary output. To further protect the urothelium (prevent hemorrhagic cystitis), uromitexan (Mesna®) 800 mg/m^2 is applied 15 minutes prior to the cyclophosphamide infusion, as well as 3, 6 and 9 hours after start of the cyclophosphamide infusion. Since neurogenic bladder with delayed emptying is common, a foley catheter is placed in patients with a history of urine retention.

Days 5-10: Granulocyte colony stimulating factor (filgrastim) 5 mcg/kg body weight/day sc in the evening. Acetaminophen (paracetamol) or mild oral opioids are acceptable as on demand medication against filgrastim-associated pain in the skeleton and soft tissues.

Day 11 and until apheresis is discontinued: Granulocyte colony stimulating factor (filgrastim) 5 mcg/kg body weight x 2 sc/day. Daily measurements of CD34+ counts in peripheral blood. Apheresis begins according to local routines, and continues until a minimum of 2 x 3.0 x 10^6 CD 34+ cells/kg body weight is obtained. The stem cell graft is processed and stored in accordance with local routines and national regulations. Lymphocyte depletion of the stem cell graft is not yet recommended by the study officials.

The Medical Officer appointed by the official central study site should be consulted in an unexpected case of a poor stem cell mobilizer..

Interval between mobilization and conditioning
In order to avoid cumulative cardiac toxicity from cyclophosphamide, a minimum of three weeks should separate administration of cyclophosphamide for mobilization and for conditioning. A maximum interval of eight weeks is recommended.

Conditioning regime (HSCT days -5 to -1) and reinfusion of the stem cell product (HSCT day 0)

HSCT days -5 to -2: Cyclophosphamide 50 mg/kg/day will be given iv in 1000 ml of standard glucose (glucose 50mg/ml) over 4 hours. The cyclophosphamide dose is highly emetogenic, and an appropriate, combined antiemetic regime should be used[37-39]. A forced diuresis of minimum 150 ml urine/hour should be obtained by infusion of at least 3000 ml normal saline iv supplemented with 20 mg of furosemide per 1000 ml fluid, and complementary doses of 20 mg furosemide iv to obtain the required urinary output to preserve the kidney function. To prevent hemorrhagic cystitis, repeated doses of uromitexan (Mesna®) 30mg/kg over 30 minutes in 100 ml normal saline (NaCl 9%) are given 30 minutes prior to cyclophosphamide infusion, as well as 4, 8, 12, 16 and 20 hours after start of each cyclophosphamide infusion, respectively. A foley catheter should be placed in patients with a history of urine retention.

HSCT days -5 to -1: Anti-thymocyte globulin (ATG-rabbit, Thymoglobuline®) 0.5 mg/kg body weight will be given iv on day –5, 1.0 mg ATG-rabbit/kg will be given iv on day -4, and 1.5 mg ATG-rabbit /kg will be given iv on days -3,-2 and -1 over 10 hours in 500 ml of normal saline (NaCl 0.9%). Due to the risk of an anaphylactic reaction, premedicate with methylprednisolone 500 mg iv and an oral antihistamine of local choice 60 minutes prior to each ATG test dose and subsequent ATG infusion. An ATG test dose (1 ml of the ATG infusion) should always be administered at least 10 minutes before initiating the ATG infusions. Patients are instructed to remain in the ward during the entire infusion period, and an available anaphylaxis emergency kit is mandatory. An in-line 0.22 m filter should be applied for the ATG administration. Ulcus prophylaxis should also be applied during high dose steroid therapy.

HSCT day 0: Reinfusion of a minimum of 3,0 x 10^6 CD 34+ cells/kg body weight. Premedication according to local routines; oral acetoaminophen 1000 mg po and an oral antihistamine are recommended.

Additional compulsory supportive therapy:
Prednisolone:
Declining doses of Prednisolone are used to prevent ATG-associated serum sickness:

- HSCT days 0, +1 and +2: Prednisolone 60 mg x 1 po
- HSCT days +3 and +4: Prednisolone 40 mg x 1 po
- HSCT days +5 and +6: Prednisolone 20 mg x 1 po
- HSCT days +7 and +8: Prednisolone 10 mg x 1 po.
- If fever or other signs of serum sickness: A supplement of metylpredisolone (Solu-medrol) 250 mg iv (followed by 125 mg iv/day for 2 days) is considered in addition to broad spectrum antibiotics if consistent fever >38^{0}C. Fever or other reactions may also result in neurological deteriation in MS-patients, and thus should be immediately addressed according to site routines[36].

Antibiotic prophylaxis[36]:

- Gram-negative prophylaxis according to local standard, starting the latest 2 days after stem cell reinfusion (HSCT Day +2)

- **HSCT day -5** and until 6 months after transplantation: Valaciclovir 500 mg x 2 po.
- **HSCT day +2** and until 3 months after transplantation: Flukonazol 200 mg x 1 po.

- **After granulocyte recovery:** trimetoprim-sulpha 500 mg 2 tabl. x 2 po on Saturdays and Sundays for 3-6 months or 1 tabl.x 2 po three times a week for 3-6 months according to local routines.

Therapy of fever and suspected or documented infections:
Microbiological specimens (blood cultures, urine and nasopharyngeal aspiration viral tests) should immediately be obtained if fever or other signs of infection (may be subtle in neutropenia), followed by prompt inititation of broad-spectrum iv antibiotic medication according to site routines. CMV and/or EBV reactivations (indicated by PCR results and/or clinical signs) should also be preemptively treated according to national/local/study site policies and protocols[36].

ATG-associated serum sickness (see above) or emerging bone marrow regeneration should also be considered and dealt with in febrile episodes, but should not exclude or replace broad spectrum iv antibiiotics for suspected or documented infections.

Blood product transfusions:
Platelets and erythrocyte transfusions should be administered according to study site policies and protocols. Blood products should be irradiated[36].

Cyclophosphamide-associated hemorrhagic cystitis:
Hemorrhagic cystitis should be suspected if hematuria and/or painful miction (urination) during or following cyclophosphamide infusions. Suspected hemorrhagic cystitis should be investigated and treated according to transplant study site procedures.

Revaccination schedule:
Revaccinations should be performed after HSCT. Recommendations provided in Appendix B should be adjusted at each study site according to national guidelines.

5.2.3 STUDY ARM B (alemtuzumab):

Premedication (prior to every alemtuzumab infusion):

a. Cetirizine 10 mg po or similar oral antihistamine
b. Methylprednisolone 1000mg iv in 100ml 0.9% saline prior to alemtuzumab infusion
c. Acetaminophen 1000 mg po prior to alemtuzumab infusion

Alemtuzumab 12 mg iv daily on 5 consecutive days at first alemtuzumab treatment cycle, followed by 3 consecutive days at the second alemtuzumab treatment cycle 12 months later.

Around 3% of patients treated with alemtuzumab experience serious infusion reactions. The patient should be monitored with measurement of blood pressure and pulse every hour during infusion. After each infusion with alemtuzumab, the patient should be observed for 2 hours for infusion associated reactions. Resources for the management of anaphylaxis or serious reactions should be available. The infusion should be stopped if any of the following occur: Hypotension (systolic blood pressure <90 or a decrease of >10mmHg from baseline if baseline systolic blood pressure <90), Persistent high grade fever, oxygen desaturation, dyspnoea, back pain, pruritus, restlessness, or other subjective complaints). The most common infusion reactions could be treated as follows: Hypotension: Isoplex 500mls followed by 0.9% sodium chloride IV bolus 1L IV over 30 minutes. Rigors: chlorphenamine 10mg IV. Fever: paracetamol 1g by mouth. Dyspnoea, back pain, pruritus, O2 desaturation: 100% Oxygen through a non-rebreathing mask followed by hydrocortisone 100mg IV and chlorphenamine 10mg IV. Consider 0.5ml epinephrine (adrenaline) 1:1000 intramuscularly. If infusion reaction symptoms completely resolve and the patient is back to baseline, re-challenge with alemtuzumab but at a slower infusion rate, doubling the infusion time.

Antiviral prophylaxis:

Acyclovir 200mg po twice daily, beginning at the first day of alemtuzumab infusion and continuing for 1 month after each alemtuzumab treatment cycle.

Discharge if stable after a 2-hour monitoring period: Vital signs, heart rate and blood pressure. Extended monitoring duration when indicated.

5.3 Duration of therapy

The planned duration of therapy is stated in section 5.2

Duration of therapy may deviate from what is planned if an intercurrent illness effects the safety of the patient, the ability to administer treatment, or the primary study endpoints. Fertility measures implemented for women of childbearing potential may postpone initiation of stem cell mobilization for up to 2-4 weeks.

5.4 Premedication and monitoring

Premedication and washout will be performed as indicated in section 5.1

5.5 Concomitant medication, restrictions and rescue therapy

Concomitant medication related to MS study treatment is stated in section 5.2.

All other concomitant medication (incl. vitamins, herbal preparation and other "over-the-counter" drugs) used by the patient will be recorded by the Investigator in the patient's medical record and eCRF. Herbal preparations should be avoided for the last month before start of treatment procedures (uncertainties regarding possible side effects on treatment medications and stem cells). Pain medication other than acetaminophen and po opioids should not be used 2 weeks prior to stem cell mobilization due to possible adverse effects on stem cell function by a variety of "pain killers".

5.5.1 Restricted therapy

Prohibited therapy in both study treatment arms: Natalizumab, fingolimod, dimetylfumurat, glatiramer acetate, interferon beta medications, teriflunomide, and alemtuzumab if administered outside the study.

In Arm A which includes cyclophosphamide, concomitant administration and dosages of agents inhibiting or inducing CYP450 may alter the treatment effect. The risk for CYP450 induction or inhibition must be carefully considered prior to or during concomitant administration of known inducing and inhibiting agents, including; amiodarone, aprepitant, bupropion, ciprofloksacin, azoles (including flukonazol in daily doses >150 mg), klaritromycin, prasugrel, sulfonamides, telitromycin, rifampicin, fenobarbital, karbamazepin, fenytoin, St. John's Wort and systemic corticosteroids.

MS-relapse treatment with a 5-day course of iv or per oral methylprednisolone is permitted by the study protocol. Apart from immunomodulatory MS treatment (see section 5.1 for wash out), no cytotoxic or immunosuppressive treatments or drugs other than the study medications can be used during the last six months prior to entry or during the trial, and the patient starting such medication will be excluded.

5.5.2 Rescue medication, emergency procedures and additional treatments

During the study period, and in particular after recent discharge from hospital, the patient should without hesitation contact the study site or a local emergency ward if signs of infections or any other sign of altered general condition.

It is essential for optimal interpretation of the study results that the patients are informed to contact their regular neurologist or their study PI/co-PI within three days in the case of a suspected relapse (MS attack).- The patient

must undergo a neurological evaluation within 7 days from the onset of relapse symptoms. If the treating physician decides that the patient has a possible relapse, the patient should without undue delay be referred for an unscheduled relapse visit at a defined study site including a quantitative neurological examination, EDSS scoring and MRI. If the relapse is considered to impede neurological function, the patient is treated with iv or oral methylprednisolone 500 or 1000 mg daily for 3 or 5 consecutive days according to local routines.Patients with aggressive attacks should be discussed with the CI/NC/PI before local initiation of high dose steroid treatment.

5.6 Drug compliance and accountability

All study treatments are administered as intravenous therapy. The study drug is administered by health care personnel and the patient is admitted to hospital during treatment. Compliance is therefore expected to be close to 100%.

Distribution, return, accountability, batch numbers and destruction of the study drug must be logged and filed in the ISF. Internal procedures at the hospital may be followed if fulfilling GCP/GMP requirements.

5.7 Drug labeling, storage and supply

The investigational product will have a label permanently affixed to the outside and will be labeled according with ICH GMP and national regulations, stating that the material is for clinical trial / investigational use only and should be kept out of reach of children. For detailed description of the label, please refer to the ISF.

Study medication must be stored under recommended storage conditions indicated on the label. A temperature log must be maintained by the investigator/pharmacist to make certain that the drug supplies are stored at the correct temperature.

The products have a marketing authorization, is routinely ordered by the pharmacy and will be dispensed from the pharmacy's own stock.

5.8 Subject numbering and assignment to treatment groups

Each subject is identified in the study by a unique subject number that is assigned through the eCRF system. When a subject signs the Informed Consent Form he/she is considered enrolled into the study as a screened patient. Patients not eligible for randomization after screening will be registered as Screening Failures in the eCRF. Once assigned the subject number cannot be reused for any other subject.

5.9 Fertility related procedures

Due to the chemotoxicity of cyclophosphamide, counselling regarding fertility conserving measures (at Visit 3) is recommended for both females and males randomized to the study. Fertility conserving measures (i.e. sperm, oocyte and/or ovarian storage) are performed according to national guidelines and must be completed prior to start of stem cell mobilization at Visit 4.1.

6 STUDY PROCEDURES

6.1 Details of trial procedures by visits

The patient information and informed consent procedures may take place prior to the screening visit (but within study window), or at the day of screening visit. The patient should be given ample time to ready through and consider participation in the study before signing the Informed Consent Form. No trial procedures should be done unless the patient has in writing consented to taking part in the trial.

The study will consist of the following periods; screening, pre-transplantation/evaluation, randomization, treatment, and follow-up phases. All trial related procedures at selected visits will be done according to the Flow Chart with footnotes, and per details provided in the sections below.

All patients are to adhere to the visit schedule as specified in the Flow Chart, and if a visit is re-scheduled, subsequent visits should follow the original visit date schedule (one month is defined as 28 calendar days).

6.1.1 Screening

No trial procedures should be done unless the patient has consented to taking part in the trial.

Screening (Visit 1) of the patients will take place at participating study sites. Once the patient has consented to trial participation, he/she is considered to be enrolled in the trial and have started screening. The patient should be registered in the enrollment log and in the eCRF as a screened patient.

All eligibility criteria should be assessed together with relevant baseline parameters prior to study inclusion (inclusion/exclusion criteria). If the patient meets the entry criteria, Visit 2 should occur as soon as possible once it has been confirmed that the patient is eligible to continue.

Patients who fail screening (i.e. fail to meet one or more of the inclusion criteria, and/or meet one or more of the exclusion criteria) following Visit 1 procedures should be registered as a screening failure in Viedoc™. If the patient does not meet the entry criteria, the patient will be followed and treated according to national/local clinical treatment guidelines.

6.1.2 Randomization visit

Randomization will occur at Visit 2 using eCRF after confirming that all inclusion criteria are still fulfilled, but no exclusion criteria are fulfilled. The randomization visit (Visit 2) can be performed as a Phone Visit if there are no clinical relevant changes for the patient since the screening visit (Visit 1). Adverse events and concomitant medication should be documented and registered in the eCRF.

For patients currently being treated with natalizumab, fingolimod, dimetylfumurat, glatiramer acetate, interferon beta-1a/1b, teriflunomide, or alemtuzumab, please refer to section 5.1 for details regarding washout of the immunomodulatory treatments.

6.1.3 Pre-transplantation evaluation

Arm A - Patients randomized to HSCT

All patients should have a full physical examination at both pre-treatment visits (Visit 3). Comorbidities, concomitant medication, and any adverse events must be reported (see section 8).

Pre-transplantation evaluation: Before start of stem cell mobilization and harvesting, pre-transplantation information (oral and written) and clinical evaluation should be performed by a transplant specialist/hematologist

in order to ensure that the patient is physically and mentally eligible for HSCT. Critical organ tolerabilities for HSCT are evaluated by blood tests (hematology, clinical biochemistry, liver tests, thyroid status, viral serology), chest X-ray, lung function tests (spirometry incl. DLCO), echo cardiography, and dental examination (to exclude or eradicate potentially infectious oral foci prior to start of treatment). Also, the patients should be offered fertility counselling to decide whether fertility measures should be performed before start of stem cell mobilization.
Minimum criteria for respiratory and cardiac functions[36] must be fulfilled;

- FEV1/FVC > 60% of predicted after bronchodilator therapy
- DLCO > 50% of predicted
- Resting LVEF > 50 %

If the transplant specialist/hematologist finds that the patient is eligible for autologous HSCT preparations for stem cell mobilization/harvesting can start. Patients not found eligible for HSCT after the pre-transplantation evaluation will be discontinued from study treatment and treated according to standard guidelines.

Fertility related procedures: Before start of treatment and/or treatment related procedures, all patients (men and female) should have blood samples collected for fertility hormone status for long-term storage in Biobank Haukeland for future research. Fertility conserving measures according to individual preferences and in line with national guidelines must be completed prior to start of stem cell mobilization (Visit 4.1). For male patients: collection of sperm for storage. For most female patients: start of hormone therapy for fertility conserving measures, followed by harvesting and storage 2-4 weeks later.

Arm B - Patients randomized to alemtuzumab

Patients randomized to alemtuzumab will not undergo supplementing clinical pre-treatment visits after randomization (Visit 3 will therefore be omitted), before returning for Visit 4.1 to start study treatment.

6.1.4 Treatment and follow-up period

Patient reported outcome forms (PROs) should be filled in at the start of the visit, physical examination and laboratory assessments must be done prior to administration of any study drugs or start of study treatment. PROs will be available both in paper and electronic format.

If any additional treatment is considered necessary for the patient's welfare during the treatment period it may be given at the investigators discretion (see section 5.5 for restricted medication).

Arm A - Patients randomized to HSCT
If the patient is considererd eligible for autologous HSCT (by pretransplantation evaluation), procedures for stem cell mobilization/harvesting, conditioning and HSCT are initiated.

Hospital stays I and II (outward setting in some study hospitals): For stem cell mobilization most patients will be hospitalized for 2(-3) days while receiving cyclophosphamide and standard supportive medication for mobilization of stem cells**.** This is followed by daily subcutaneous injections of granulocyte colony stimulating factor (Filgrastim®)from Day 5 until finalized stem cell harvesting. On Day 10 or 11 the patient returns to the study hospital for stem cell harvesting. Details regarding dosing and administration of the mobilization regime are provided in Section 5.2. Mobilization and harvesting procedures and any events that occur are registered on Visit 4.1 in the eCRF.

In order to avoid cumulative cardiac toxicity from cyclophosphamide, a minimum of 3 weeks should separate administration of cyclophosphamide for mobilization and conditioning. A maximum interval of 8 weeks is recommended.

Hospital stay III: Three to six weeks after harvesting, the patient is hospitalized for about 3 weeks to perform conditioning, stem cell reinfusion (HSCT) and a protective isolation period. Detailed instructions on administration of study treatments during this stay are provided in Section 5.2 and in Appendix A (a schematic overview of the patient flow). The isolation period usually lasts for 5-10 days. Routine blood sampling will be performed daily as part of the patient monitoring during the hospital stay III for conditioning, reinfusion and isolate period (3 weeks). Daily tests: Hgb, leucocyte count with differentials, thrombocyte count (2 times daily for 5 days while receiving ATG), CRP, creatinine, sodium, kalium. Three times a weeks: blood cross-match, ALP, GT, ASAT, ALAT. bilirubin (and supplementing liver tests on demand if suspected liver toxicity). Once a week: p-CMV and p-EBV PCRs. The patient is discharged from hospital according to local routines, but the patient should as a minimum have a reconstituted bone marrow function, be off parenteral antibiotics and other supplementary iv therapy and be capable of performing adequate daily activities of life. Procedures and any events that occur are registered on Visit 4.2 in the eCRF.

Short term follow-up after HSCT (post-transplantation control visits): After discharge from hospital, weekly follow-up is required until Day +100 after HSCT for safety monitoring (blood test and consultation) and clinical care (see also section 7.1.8). Weekly blood tests and consultations should be under the direct control of a transplant specialist or combined care between transplant specialist/hematologist and referring neurologist or a general practitioner when a patient is considered clinically stable by the transplant specialist (intervals may be extended by the transplant specialist after the first 6 weeks). Monthly blood pregnancy tests are required.

The first post-transplant study visit is performed at day +100 after HSCT at designated HSCT-study sites. According to the study design the HSCT day +100 visit is considered to "parallel" the 3 months study visit in arm B (Visit 5).

Long-term follow-up (**study visits** at HSCT/central study site(s)): All patients will return for study follow-up visits, endpoint evaluation and collection of study data according to Flow Chart at 6, 12, 18, and 24 months after Treatment day "0" (and after 30,36, 42,48, 54 and 60 months during the study extension).

Between study visits patients should have the following safety laboratory tests analyzed locally

- Every third month (at least):
  - Hematology: HgB, leucocytes with cell differentials, thrombocytes
  - Clinical chemistry: serum sodium, potassium, bilirubin, CRP, creatinine
  - Thyroid gland: TSH, free T4
  - Urine strip analysis

- Monthly:
  - Serum human chorionic gonadotropin (hCG) pregnancy test (required only until 12 months after last administration of alemtuzumab

An unscheduled visit should be performed in case of abnormal findings indicating MS relapse or disability progression (as per protocol definitions, see section 2.2), suspected treatment complication, any acute illness of undetermined cause, or at the discretion of the Investigator. Close communication between the patients and local hospital staff involved in weekly/quarterly safety follow-up is crucial for timely identification and reporting of events in the study.

Fertility measures: For women with fertility conserving measures prior to HSCT treatment, transvaginal ultrasound of ovaries will be performed at 1 year and 2 year follow-up visits (Visit 7 and 9) to investigate potential impact of cyclophosphamide on fertility. For men, sperm sampling will be performed at 1 year and 2 year follow-up visits (Visit 7 and 9) to investigate potential impact of cyclophosphamide on fertility.

Arm B - Patients randomized to alemtuzumab
After randomization to arm B, patients will start alemtuzumab treatment course 1 at Visit 4.1 (Treatment day "0"), followed by study visits at 3 and 6 months (Visits 5 and 6, respectively).

At 12 months (Visit 7), the patient receives alemtuzumab treatment course 2. See section 5.2 for dosages and administration of alemtuzumab and standard supportive therapy.

Short and long term **study visits** after discharge:
All patients will return for study follow-up, endpoint evaluation and collection of study data according to Flow Chart at 6, 12, 18 and 24 months after Treatment day "0" (and after 30, 36, 42, 48, 54 and 60 months during the extension study).

Between study visits patients should have the following safety laboratory tests analyzed locally:

Monthly laboratory tests until 60 months after the last alemtuzumab treatment cycle:
- Hematology: HgB, leucocytes with cell differentials, thrombocytes
- Clinical chemistry: serum sodium, potassium, bilirubin, CRP, creatinine
- Urine strip analysis
- Serum human chorionic gonadotropin (hCG) pregnancy test (required only until 4 months after last administration of alemtuzumab)

Thyroid gland function (every 3 months until 60 months): TSH, free T4.
Gynecological examination including HPV/cervical dysplasia screening annually.

An unscheduled visit should be performed in case of abnormal findings indicating MS relapse, suspected treatment complication, any acute illness of undetermined cause, or at the discretion of the Investigator. Close communication between the patients and local hospital staff involved in weekly/quarterly safety follow-up is crucial for timely identification and reporting of events in the study.

In case the study extension will not be performed, patients in both study arms should be followed up long-term according to standard of care by their treating neurologist. For arm B this also includes the monthly laboratory tests until 48 months after the last alemtuzumab treatment cycle, as specified above in this section.

6.1.5 Unscheduled visits

In addition to the scheduled study visits, patients may have unscheduled study visits due to a new, confirmed MS activity event (clinical relapse, disability progression or MRI findings per protocol definitions, see section 2.2), a suspected treatment complication, any acute illness of undetermined cause, for other reasons, or at the discretion of the Investigator. Data collected during unscheduled study visits will be recorded in the unscheduled visit eCRFs. Additional procedures and investigations should be performed as indicated by the clinical situation.

Patients must be instructed to immediately report new neurological symptoms, re-occurring or worsening of previous symptoms to the Investigator. If a patient reports symptoms that may be consistent with relapse, an unscheduled study visit must be performed as soon as possible (whenever possible within 7 days of onset of the symptoms).

6.1.6 Withdrawal and early study discontinuation

If a patient refuses to attend all originally planned study visits, but agrees with vital status assessment, the latter will be conducted preferably according to visit schedule as in the Flow Chart, but as a minimum at the 2 year visit (Visit 9), and at the 5 year visit (Visit 15) for the planned study extension.

6.1.7 End of study period

If a patient discontinues study participation early (prior to Visit 7 or Visit 9) for whatever reason, he/she should return to the study site for the End of Study assessments.

For patients completing study per protocol, the last scheduled visit will be at 2 years follow-up, and for the extension study 5 years follow-up.

6.1.8 Switch to other therapy

Patients may be offered treatment corresponding to the opposite study treatment arm or start other MS medication if they experience significant new inflammatory disease activity (see Section 2.2) during the study treatment period. Significant inflammatory disease activity during the treatment period is a protocol-defined disease activity event (refer to section 2.2), but must include both a relapse and protocol defined MRI activity and/or disability progression. Start of therapy corresponding to the treatment offered in the opposite study treatment arm will need to wait for 12 months after the latest alemtuzumab treatment or 12 months after conditioning in the HSCT treatment arm.Earlier rescue treatment should be discussed with the CI.

A follow-up study visit (scheduled or unscheduled) prior to cross-over is required to assess the patients clinical status and safety parameters.

6.2 Procedures for discontinuation

For patients who stop study treatment after Visit 4.1 (only applicable for arm B), or who wishes to withdraw from further study participation, the following should be performed whenever possible:

End of Study (EOS/EOXS) visit procedures including completion of PROs, physical examination, vital signs, neurological examination, MRI, recording of adverse events and concomitant medication, sampling of blood for safety laboratory parameters and biobanking, CSF and stool sample.

Patients discontinuing study treatment should continue to follow the original visit schedule.

6.3 Laboratory tests

Collection of biological material must be done at timepoints as specified in the Flow Chart. The local study site laboratory will be used for the analyses of hematology, biochemistry and serology specimens collected, sperm analysis (at selected sites only and according to WHO standard) and for serum hCG pregnancy test.

Biological material for biobanking will be collected and shipped to Biobank Haukeland for long-term storage. Details describing collection, processing, shipment and storage of samples are available in the ISF.

7 ASSESSMENTS

7.1 Assessment of efficacy

In order to confirm NEDA or evidence of new disease activity events during the study treatment and observation periods, the following clinical and radiological parameters and examinations should be performed at scheduled and unschedules study visits):

7.1.1 Lesions and atrophy

MRI will be performed at timepoints indicated in the Flow Chart. Measures of new lesions, enlargement of existing lesions, the total lesion load, and changes in brain volume will be done at a central MRI reading site. Procedures for obtaining and reading of MRI images will be filed int the ISF.

7.1.2 Clinical MS relapse

A relapse should without undue delay be confirmed by an assigned neurologist (PI or co-PI at a study site at a scheduled study visit (if a suspected relapse occurs within a few days before a scheduled visit) or at a supplementing, unscheduled study visit, including a full clinical neurological examination with EDSS scoring followed by MRI, preferably within 7 days from onset of symptoms.

7.1.3 Expanded Disability Status Scale (EDSS)

Disability progression will be assessed using EDSS at timepoints indicated in the Flow Chart[40]. For assessment of EDSS, see Appendix C.

7.1.4 For individual patients EDSS scores should preferably be assessed by the same neurologist (PI or co-PI) throughout the study. EDSS certification is compulsory for all study personnel performing EDSS scorings at defined study visits, and copies of relevant certificates should be placed in the ISF.Patient reported outcomes (PROs)

Assigned investigators or other designated site-personnel should ensure that the patient has access to a quiet area at the study site where the patient can record her/his answers in the questionnaires. If a patient cannot give or decide upon a response to a specific questions no response should be recorded. The study site investigator or designated site-personnel should check that all items have been completed by the patient, but the patient response to each item should not be scrutinized . Instructions to patients are included in the questionnaires.

EQ-5D-5L

Health related quality of life will be assessed using the EQ-5D-5L (see Appendix D) according to the Flow Chart[41]. EQ-5D-5L is a standardised instrument to measure of health outcome. It is designed for self-completion by the patients[41].

The EQ-5D-5L self-report questionnaire essentially consists of 2 pages comprising:

- the descriptive system (five dimensions of health; namely mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension comprises three levels (no problems, some/moderate problems/extreme problems).
- the EQ-VAS (visual analogue scale) which records the patient's self-rated health status on a vertical graduated (0 – 100) VAS.

In Norway, as a part of an extended QoL assessment and a health economic evaluation, the EQ-5D-5L questionnaire will be supplemented with questionnaires regarding the overall contentment of the patient, employment status and participation in social life.

Multiple Sclerosis Impact Scale (MSIS)

The Multiple Sclerosis Impact Scale (MSIS-29) is a 29-item self-report measure comprising 20 items associated with a physical scale and 9 items associated with a psychological scale.

Patients (or their proxies) are asked about the impact of MS on day-to-day life in the last 2 weeks. All items have 5 response options from 1 (not at all) to 5 (extremely). Each of the 2 scales are scored by adding up the responses across items, then converting to a 0 to 100 scale, where 100 indicates greater impact of disease on daily function (worse health).

Reliability and validity evidence have been obtained in multiple samples of people with MS from disability levels of 0 to 9.5 on the Expanded Disability Status Scale. The MSIS-29 is responsive to intervention, with a change score of about 8 on the physical scale or about 6 on the psychological scale having moderate to high sensitivity and specificity for patients, indicating whether they had improved or not[42].

Fatigue Severity Scale (FSS)

The Fatigue Severity Scale (FSS) is a method for evaluating fatigue in multiple sclerosis and other neurological conditions.

The Fatigue Severity Scale (FSS) is designed to differentiate fatigue from clinical depression, since both share same symptoms. Essentially, the FSS involves answering a short questionaire that requests a rating of the patients' subjective level of fatigue.

7.1.5 9-Hole Peg Test and Timed 25-foot walk

9-HPT and T25FW are two out of three variables recommended as primary measures in the Multiple Sclerosis Functional Composite (MSFC)[43]. 9-HPT is a quantitative measure for upper extremity function, whereas the T25FW is a quantitative measure for lower extremity function[44].

7.1.6 The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

The BICAMS is a brief cognitive assessment that can be used also in study sites with staff members with no neuropsychological training[45] The tests address specific cognitive deficits that are common in MS patients, and the scales were chosen also for their psychometric qualities (reliability, validity and sensitivity)[46]. Tests must be administered during daytime, in a standardized manner, and in a quiet room. The order of tests will be fixed: the Symbol Digit Modalities Test (SDMT),Brief Visuospatial Memory Test-Revised (BVMT-R), and California Verbal Learning Test-II (CVLT-II).

7.2 Assessment of safety and tolerability

Safety will be monitored by the assessments described below and reported AEs. Significant findings present prior to the signing of informed consents must be included in the relevant medical history/ current medical condition page of the eCRF. For details on AE collection and reporting, see Section 8.

For the assessment schedule see Flow chart.

7.2.1 Physical examination

A full physical examination will be performed by the investigator and includes the following; skin (colour, rash, lesions, oedema), lymph nodes, blood pressures, heart rate, body temperature, body height/weight, oral inspection, lung/heart/abdominal examination, peripheral pulse. Documentation of clinical parameters obtained by physical examinations must be part of the source documents available at each study site.

7.2.2 Vital signs

Vital signs including body temperature, blood pressure and heart rate will be measured at all study visits after the patient has rested for five minutes in seated position. The recordings should be performed on the same arm, preferably using a mercury sphygmomanometer or a validated certified blood pressure recording instrument. The recordings should be documented in source documents and entered into the eCRF.

7.2.3 Body height and weight

Body height and weight will be measured at the screening visit (Visit 1) according to the following restrictions:

- weight is registered after bladder voiding
- shoes and coat/jackets should be taken off
- pockets should be emptied of heavy objects (i.e. keys, coins etc.)

Registrations of body weight are repeated with the same restrictions before ordering the mobilization and conditioning regimens in order to facilitate adequate adjustments of doses of all relevant medications (study drugs and weigth-dependet supportive care) of the mobilization and conditioning regimens in study arm A.

7.2.4 Safety laboratory parameters

All safety laboratory parameters will be collected at the timepoints as indicated in the Flow Chart, and include hematology, liver enzymes/parameters, clinical chemistry, thyroid status and serology. All safety parameters evaluated during the study are listed in Table 7.2.2:1 below. The samples will be analysed at the local laboratory at each study site. The respective reference ranges must be provided to the central study administration for uploading into the eCRF.

Table 7.2.4:1 Safety laboratory parameters – blood, serum, plasma

Hematology	
• Hemoglobin • WBC/leukocytes	• Platelet count / thrombocytes • Differentials: neutrophils, eosinophils, basophils, monocytes, lymphocytes
Liver enzymes/parameters	
• ALAT (alanine transaminase, SGPT) • ASAT (aspartate transaminase, SGOT)	• Alkaline phosphatase • GT (glutamyl transferase) • Bilirubin total, fractionated if increased
Clinical chemistry	
• Albumin • Calcium • Creatinine • CRP	• Magnesium • Potassium • Sodium
Thyroid status	
• TSH (thyroid stimulating hormone)	

- Free T4

Pregnancy testing will be performed in serum in female patients of child-bearing potential only. For patients in study treatment arm A, pregnancy testing will be performed monthly from start of conditioning and until 12 months after last administration of cyclophosphamide. For patients in study treatment arm B pregnancy testing will be performed monthly from start of treatment with alemtuzumab until 4 months after the last study administration of alemtuzumab.

The safety measurement schedules differ somewhat in arm A and arm B. See section 6.1.4 for detailed information about study and non-study safety follow-up.

7.2.5 Serology laboratory parameters

Serology parameters are analyzed at Visit 1 to rule out active or chronic viral infections as part of the eligibility evaluation. EBV and CMV should be checked weekly until Day +100.

Table 7.2.5:1 Serology laboratory parameters – serum

Serology	
• Quantiferone	• Varicella zoster virus IgM/IgG
• Hepatitis Bs-virus ag	• CMV ab
• Hepatitis Bs-virus ab	• EBV ab
• Hepatitis Bc-virus ab	• Toxoplasmosis ab
• Hepatitis C virus ab	• HTLV ab
• HIV ab	• Syphilis TP ab
• Herpes simplex virus ag/ab	

7.2.6 Chest X-ray

Chest X-ray is performed at the screening visit (Visit 1) to rule out presence of tuberculosis or other relevant pulmonary diseases.

7.2.7 Arm A: Pretransplant tolerability investigations

Ecco cardiography, lung spirometry with DLCO and dental/oral examination will be performed as part of the pretransplantation evaluation in arm A in order to rule out ciritical organ dysfunctions and identify and eradicate or diminish potenicially infectious foci before start of HSCT-associated chemotherapy regimens.

7.2.8 Karnofsky Performance Status

The Karnofsky Performance Status will be completed by patients in the study arm A to describe general physical performance. The Karnofsky score is not linked to a study endpoint, but is a requested score when updating the European Bone Marrow Transplantation (EBMT) register.

All study sites are requested to report relevant registrations in study arm A to the EBMT.

7.3 Research assessments

A wide array of immunological parameters and other biomarkers will be performed in various patient samples.

7.3.1 Biobanking

Participation in sampling of whole blood, serum, and plasma for biobanking is mandatory and a prerequisite for participation in the study. Information concerning biobanking of these samples are included in the main ICF for the study. Detailed instructions on sampling, sample handling, shipment and storage of samples are provided in the ISF.

Biobanking of CSF, DNA, stool and sperm samples (the latter applicable for male patients in treatment arm A only) and the transvaginal ultrasound procedure (applicable for female patients in treatment arm A only) are voluntary and not a prerequisite for study participation. A separate informed consent form will be provided, and in accordance with ethical and regulatory requirements, this must be signed before sampling is executed..

Biological samples will be stored in the Biobank Haukeland at HUS, and will only be used as decided by the PMC for research related to MS pathogenesis and effects of the study treatments.

Measures are implemented to comply with applicable rules for collection, biobanking, and in particular for future use of biological samples and clinical data obtained during this study.

7.3.2 Methods and timing of sample collections

Sampling will be performed at time-points indicated in the Flow Chart. Some of the samples will only be collected from patients at selected sites indicated with an "*****" in the text below. Details for sample collection, processing and storage are provided in the laboratory manual.

Whole blood:
From less than 10 mL to a maximum of 120 mL blood will be drawn for preparation of PBMC, buffy coat, serum and plasma at each timepoint for sample collection as described in Flow Chart.

Preparation of serum:
Approximately 12 mL whole blood will be drawn into untreated serum separator tubes allowed to clot for 50-60 min, and thereafter centrifuged. The serum will be split into 8 x 500 µL . The will be stored at -80^{O}C in Biobank Haukeland.

Preparation of plasma:
Approximately 12 mL blood will be drawn into EDTA collection tubes, centrifuged and the plasma split into 8 x 500 µL aliquots, and stored at -80^{O}C in Biobank Haukeland.

Cells from blood:
8 mL whole blood will be drawn into anticoagulant collection tubes, split in 8 x 1 mL aliquots, fixed and stored at -80^{O}C.

DNA banking:
Approximately 12 mL blood will be drawn into an EDTA tube as described for "Preparation of Plasma". The buffy coat will be aliquoted into 2 x 500 µL and stored at -80^{O}C in Biobank Haukeland. Donation of buffy coat for DNA analyses is optional and will be done only at one visit.

***** *Preparation of PBMC:*
At different study visits approximately 60 mL (Visit 4.1 and Visit 5), 40 mL (Visit 4.2) and 70 mL (Visit 3.1, Visit 7, and thereafter biannually), 90 mL (Visit 6) whole blood will be drawn into anti-coagulant tubes, processed and aliquots of approximately 15-20 million cells per mL will be cryopreserved. These cells will be cryopreserved at -196^{O}C.

CSF:

Approximately 12 mL CSF will be collected in sterile tubes and centrifuged at low speed to preserve the cells. The first 2 mL will be used for routine analysis. The supernatant will be aliquoted into 8 x 500 µL and stored in -80^{O}C in Biobank Haukeland. The cells will be fixed and stored at -80^{O}C.

Stool:
A portion (approximately 10 g) of the first stool of the day will be collected, processed, split into 8 x 800 µL aliquotes and frozen at -80 °C in the biobank.

*Sperm:
Participants will be asked to abstain from ejaculation for 2 consecutive days and then to masturbate without lubricant into a glass specimen container.

* Stem cell product:
Approximately 1 mL of the stem cell product will be collected from patients treated at HUS.

7.3.3 Cerebrospinal fluid

CSF analyses will include, but are not limited to, T cell receptor sequencing, B cell receptor sequencing, isoelectric focusing, quantification of neurofilament light chain levels (ELISA) and cytokines, proteomic study for potential other biomarkers for therapeutic response, but also other analyses in the future for upcoming scientific purposes to better understand the nature of the MS disease and/or the human responses to the applied study treatments.

7.3.4 Fertility measures

Sperm sampling will be performed at the 1 year and 2 year follow-up visits (Visit 7 and 9) to investigate potential impact of study treatment on male fertility. Specimen volume, consentration and pH will be measured. Specimens will also be inspected for motility and morphology.

Transvaginal ultra sound will be performed to investigate potential impact of study treatment on female fertility.

Fertility related hormones will be analyzed in male and female patients.

7.3.5 Microbiota analysis

The microbiota of stools will be analysed by DNA extraction and purification, library preparation, 16S rRNA gene sequence analysis. Other analyses might also be performed if new knowledge indicates scientific interest to better understand the nature of the MS disease and/or the human responses to the applied study treatments.

7.3.6 Blood cells

To investigate characteristics of the treatment mechanisms and identify markers of therapeutic response, cells from whole blood will be collected pre- and post-treatment. Mass cytometry will be used to study immune reconstitution and immune ablation during treatment. Further, these cells will be used to sequence T-cell and B-cell receptors.

Immune monitoring will be performed in PBMCs, serum and CSF as recommended by EBMT[24]. Cytokine profiles will be detected by flow cytometric analyses of patient serum and CSF before start of treatment and at regular intervals after treatment, and before start of other immunomodulatory MS-treatment in patients with (new) breaktrough MS-activity.

Additionally blood for PBMC with separation of CD4 and CD8 will be analyzed immediately using antibody-covered magnetic beads.

7.3.7 Cells from graft samples and blood during apheresis procedure

During mobilization 16 mL whole blood will be drawn from patients treated at the central study site (HUS) to perform cell analyses. An aliquot of the graft sample will also be analyzed with various immunological analyses.

7.3.8 Analyses of plasma for virus activation of IgG response

Several studies have shown an association between first appearence (or relapse) of MS and high levels of humoral immune activation against Epstein-Barr virus (EBV) - in particular titers of EBV nuclear antigen-1[47]; EBNA[47]. A putative mechanism for this relationship is ”molecular mimicry”, i.e. a cross activation of EBV peptides and human cellular epitopes. However, the role of EBV in MS is not confirmed, and an enhanced IgG reactivity could alternatively reflect EBV-specific antigenic exposure.

EBV antibodies in serum from both groups of patients will be analyzed retrospectively. Plasma, routinely stored in the biobank at regular intervals (and at relapse), will be used for analyses of EBV antibodies. As controls, antibody titers against other viruses with or without connection to CNS diseases will be analysed.

7.3.9 MRI

MRI will be performed at regular intervals as part of the clinical effect evaluation as specified in the primary and secondary endpoints. Other MRI endpoints related to treatment effect may be added.

7.3.10 Proteomics

Proteomics analyses are planned for the CSF samples in this project, and partially also for the plasma/serum samples (only targeted analyses). Global quantitative proteomics where as many as possible of the proteins in the CSF of all samples to be compared are identified and quantified will be used to get an overview of the proteins affected by the treatment. For the proteins of interest from these analyses, those affected by the treatment given, we will develop or establish targeted proteomics assays to enable absolute accurate quantification of up to 40 proteins in a multiplexed manner. These assays will be used to analyze new samples for verifying the initial findings and when verified they will serve as measurement of the affected biological processes in larger cohorts of various disease states and treatments to reflect patient disease status and potentially predict prognosis and treatment effect.

8 SAFETY MONITORING AND REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Each patient will be instructed to contact the investigator immediately should they manifest any signs or symptoms perceived as potentially serious.

The methods for collection of safety data are described below.

8.1 Definitions

8.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The term AE is used to include both serious and non-serious AEs.

An adverse reaction is defined as a response to a medicinal product or treatment which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product or treatment and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the medicinal product or treatment within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse and abuse.

If an abnormal laboratory value/vital sign are associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information that must be collected on the relevant eCRF.

8.1.2 Serious Adverse Event (SAE)

A serious adverse evente (SAE) is defined as any untoward medical occurrence that:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect

Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious. Hospitalization for administrative reason (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalization.

A pre-planned hospitalization admission (i.e. elective or scheduled surgery arranged prior to the start of treatment) for pre-existing condition, or hospitalization due to a MS-relapse is not considered to be a serious adverse event.

8.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reactions are SAEs that are unexpected as defined in section 8.2 and possibly related to the investigational medicinal product(s).

8.2 Expected adverse events

To fulfill the regulatory requirement for expedited safety reporting, the Medical Officer appointed by the Sponsor evaluates whether a particular adverse event is a known side effect of the treatment or not. Reference documents for known side effects are the current versions of the SmPCs for alemtuzumab (Lemtrada®), cyclophosphamide (Sendoxan®), anti-thymocyte globuline (ATG-rabbit, Thymoglobulin®), uromitexan (Mesna®).

8.3 Time Period for Reporting AE and SAE

For each patient the standard time period for collecting and recording AE and SAEs will begin at signature of informed consent and continue until the day of the 2 year follow-up visit (and until year 5 for the planned extension visit). If future funding allows the study extension to be performed, then AE reporting should be limited to SAEs and AEs related to study treatment during the extension period.

During the course of the study, all AEs and SAEs will be proactively registered for each patient; events should be followed up to resolution, unless the event is considered by the investigator to be unlikely to resolve due to the underlying disease. Every effort should be made to obtain a resolution for all events, even if the events continue after study discontinuation/ completion.

8.4 Recording of adverse events

If the patient has experienced adverse event(s), the investigator will record the following information in the eCRF:

- The nature of the event(s) described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).
- The duration of the event described in terms of event onset date and event ended data.
- The intensity of the adverse event (mild, moderate, severe)
- The Causal relationship of the event to the study medication, which should be assessed as one of the following:

  Unrelated:
  There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.

  Unlikely:
  There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.

  Possible:
  There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.

  Probable:
  There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.

  Definite:

There is a reasonable causal relationship between the investigational product and the AE.

- Action taken
- The outcome of the adverse event – whether the event is resolved or still ongoing.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 8.1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered as severe nausea, but is not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

8.5 Reporting procedures

8.5.1 AEs and SAEs

All adverse events and serious adverse events defined in section 8.1 will be registered in the patient's eCRF.

SAEs must be reported within 24 hours after the site has become aware of the SAE. Every SAE must be documented by the investigator. By filling in seriousness criteria on the AE page in the eCRF the SAE form is recorded in the database, and notification sent to the Medical Officer (at Sponsor). The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the individual subjects by unique code numbers assigned to the latter.

The Sponsor keeps detailed records of all SAEs reported by investigators, and performs an evaluation with respect to causality and expectedness. Based on, among other, SAE reports, the Sponsor will evaluate whether the study risk/benefit ratio associated with the study is changed. All participating study sites will be informed bimonthly of serious adverse events.

8.5.2 SUSARs

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to the Competent Authority and Ethics Committee according to national regulations. The following timelines should be followed:

The sponsor will ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authority and Ethics Committee in any case no later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days.

All other SUSARs will be reported to the Competent Authority and the Ethics Committee as soon as possible but within a maximum of fifteen (15) days of first knowledge by the sponsor.

SUSARs will be reported using the Danish Medicines Agency's e-form for electronic reporting to the European Union (EU) medicines regulatory network. The e-form is available via the web-site www.laegemiddelstyrelsen.dk.

8.5.3 Exemptions to SAE reporting

A list of serious adverse events that commonly occur in the trial population or are components of a trial endpoint are exempted from expedited reporting to regulatory agencies or ethics committees. These events are known consequences of the underlying disease, and it is not possible, based on a single case to conclude that there is a reasonable possibility that these events are caused by the study treatment. Refer to current version of SmPCs for a list of SAEs exempted from expedited reporting to authorities.

Fatal and life-threatening serious adverse reactions are NOT exempted from expedited reporting, although they are mentioned in the SmPC.

8.5.4 Annual safety report

Once a year during the study period, the Sponsor will provide Competent Authorities with an annual safety report according to national guidelines. The format will comply with national requirements.

8.5.5 Clinical study report

The adverse events and serious adverse events occurring within the study period will be discussed in the safety evaluation part of the Clinical Study Report.

8.6 Procedures in case of emergency

The investigator is responsible for assuring that procedures and expertise are available to cope with emergencies. A Medical Officer is available for clinical guidance. Contact details are provided in the ISF.

9 DATA MANAGEMENT AND MONITORING

9.1 Case report forms

The Clinical Data Management System (CDMS) used for the eCRF in this study is Viedoc™. The setup of the study specific eCRF in the CDMS will be performed by the Department of clinical research support at Oslo Univerity Hospital. The eCRF system will be FDA Code of Federal Regulations 21 Part 11 compliant.

The designated investigator staff will enter the data required by the protocol into the eCase report forms (eCRF). The Investigator is responsible for assuring that data entered into the eCRF is complete, accurate, and that entry is performed in a timely manner. The electronic signature of the investigator will attest the accuracy of the data on each eCRF. If any assessments are omitted, the reason for such omissions will be noted on the eCRFs. Corrections, with the reason for the corrections will also be recorded.

An online eLearning with detailed instructions incorporated is included in the CDMS. After database lock, the investigator will receive a digital copy of the subject data for archiving at the investigational site.

9.2 Source data

In accordance with regulatory requirements the Investigator should prepare and maintain adequate and accurate source documents and study records. Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). Changes to the data should be traceable (audit trail).

Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained.

The medical records for each patient should contain information which is important for the patient's safety and continued care, and to fulfill the requirement that critical study data should be verifiable.

To achieve this, the medical records of each patient should clearly describe at least:

- That the patient is participating in the study, e.g. by including the enrollment number and the study code or other study identification
- Date when Informed Consent was obtained from the patient and statement that patient received a copy of the signed and dated Informed Consent
- Results of all assessments confirming a patient's eligibility for the study
- Diseases (past and current; both the disease studied and others, if relevant)
- Surgical history, as relevant
- Treatments withdrawn/withheld due to participation in the study
- Results of assessments performed during the study
- WHO performance status assessments conducted as part of the study, if applicable
- Treatments given, changes in treatments during the study and the time points for the changes
- Visits to the clinic / telephone contacts during the study, including those for study purposes only
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments
- Date of, and reason for, discontinuation from study treatment
- Date of, and reason for, withdrawal from study
- Date of death and cause of death, if available
- Additional information according to local regulations and practice

A source data list will be agreed upon for each site specifying the source at a module or a variable level.

The current medical history of the subject may not be sufficient to confirm eligibility for the study and the Investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the Investigator must retrieve previous medical records.

Before providing any copy of patients' source documents to the Sponsor the Investigator must ensure that all patient identifiers (e.g. patients name, initials, address, phone number, social security number) have been properly removed or redacted to ensure patient confidentiality.

9.3 Study monitoring

The Sponsor will monitor the conduct of the study by regular visits to study sites and by in-house data quality review. The Clinical Study Monitor will check the following:

- Informed consent process
- Reporting of adverse events and all other safety data
- Adherence to protocol and treatment compliance

- Maintenance of required regulatory documents
- Drug accountability
- Facilities and equipments
- Data completion on the eCRFs including source data verification (SDV).

The Study Monitor will review the relevant eCRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required. A combination of on-site, remote and central monitoring will be implemented to direct focus and resources to the areas of greatest risk, which have the most potential impact on patient safety and data quality.

Sponsor representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study will be required.

9.4 Confidentiality

The investigator shall arrange for the secure retention of patient identification and code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site Files, etc) shall be retained and stored during the study and for at least 15 years after study closure, according to current legislation. All documentation regarding study drugs and the subject code list must be kept for 30 years after expiry date. All information concerning the study must be stored in a safe place inaccessible to unauthorized personnel.

9.5 Database management

Data management will be performed by the Department of clinical research support at Oslo University Hospital. The Data management procedures will be performed in accordance with the department's SOPs and ICH guidelines. The data management process will be described in the study specific data handling plan and the study specific data handling report after database closure.

Data entered into the eCRF will be validated as defined in the data validation plan. Validation includes, but is not limited to, validity checks (e.g. range checks), consistency checks and customised checks (logical checks between variables to ensure that study data are accurately reported) for eCRF data. A majority of edit checks will be triggered during data entry and will therefore facilitate efficient 'point of entry' data cleaning.

Data management personnel will perform both manual eCRF review and review of additional electronic edit checks to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and the issues will be reviewed manually online to determine what action needs to be taken.

Manual queries may be added to the system by clinical data management or study monitor. Clinical data managers and study monitors are able to remotely and proactively monitor the patient eCRFs to improve data quality.

All updates to queried data will be made by authorised study site personnel only, and all modifications to the database will be recorded in an audit trail. Once the queries have been resolved, eCRFs will be signed by electronic signature Any changes to signed eCRFs will be approved and resigned by the Investigator.

Adverse events and medical history will be coded from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities MedDRA. Prior and concomitant medications and therapies will be coded according to the always latest version of ATC/DDD Index.

Once the full set of eCRFs have been completed and locked, the Sponsor will authorise database lock and all electronic data will be sent to the designated statistician for analyses. Subsequent changes in the database will be restricted to written agreement between HUS and Department for clinical research support at Oslo University Hospital, Norway.

The data will be stored in a dedicated and secured area at HUS. Data will be stored in a de-identified manner, where each study participant is recognisable by his/her unique trial subject number. The data will be stored until 30 years after archiving of the Clinical Study Report.

10 STATISTICAL METHODS AND DATA ANALYSIS

10.1 Determination of sample size

The sample size for the study was estimated on the basis of previous studies on the comparators. After two years of follow-up, the proportion of NEDA after HSCT was 80 % in an observational study[17], while it was 32 % in a randomized trial after treatment with alemtuzumab[3]. The proportion of NEDA after HSCT is in this study conservatively predicted to be 64 %, representing a double percentage of NEDA compared to 32 % for alemtuzumab. A χ^2 test was used to determine the sample size using a type 1 error rate of 0.05. A sample size of 50 patients per treatment group would give a 87 % power to detect this predicted difference while assuming a dropout rate of 10 %. In a randomized RRMS treatment trial, the dropout rate was < 10 % in the alemtuzumab treatment group[3]. If there, for any reason, is a dropout rate of more than 10% in one of the treatment arms after randomization, but before first treatment, 10 additional patients will be recruited to the study and randomized in a 1:1 ratio to the two treatment arms.

This volume of patients is expected to be reached within 2 years after start of patient inclusion, based on the incidence rate of RRMS in Sweden/Denmark/Norway, which is approximately 1500 patients per year, and the current yearly rate of HSCT treatment of RRMS in Scandinavia using current (more narrow) indication criteria: approximately 50 patients[6]

10.2 Randomization

10.2.1 Allocation- sequence generation

Eligible patients will be allocated in a 1:1 ratio between the two treatment arms, using a computer randomisation procedure stratified by age, sex and country. The randomisation will be blocked within each stratum.

Details of block size and allocation sequence generation will be provided in a separate document unavailable to those enrolling patients or assigning treatments.

10.2.2 Allocation- procedure to randomize a patient

The computer-generated randomized allocation sequence will be imported into the eCRF system and made available to the investigator (and sub-investigator if authorized by the principal investigator). The allocation will not be available until the patient has signed the informed consent form and deemed eligible to participate in the study. That is, authorized personnel will only know the allocation of included patients, but not for future patients.

10.3 Population for analysis

- Intention to treat (ITT) population: All randomized patients, regardless of protocol adherence. Patients that withdraw from the study for any reason at any stage after randomization will still be included in the ITT analyses.

- Per-protocol (PP) population: Includes all patients who adhere to the protocol. Only subjects with important protocol violations (IPVs) for efficacy will be excluded from the PP population. These IPV definitions will include consideration of important violation criteria, treatment non-compliance, treatment dispensing errors and prohibited concomitant medication.

- Safety population: Includes all subjects who have received at least one dose of study medication. Subjects who withdraw from the study will be included in the safety analysis. A list of withdrawn subjects, preferably with the reasons for withdrawal, will be made.

All efficacy analyses will be performed using the ITT population. In addition, the PP population will be used in sensitivity analyses to evaluate the influence of protocol violations on the results from the ITT analyses.

10.4 Planned analyses

Prior to the main statistical analysis, the data base will be locked for further entering or altering of data. A separate statistical analysis plan (SAP) will provide further details on the planned statistical analyses. The SAP will be finalized, signed and dated prior to database lock. The treatment allocation will be revealed after the database lock and used in the statistical analysis.

There is no formally planned interim analysis.

Deviation from the original statistical plan will be described and justified in the Clinical Study Report. Amendments to plan can be done until day of Database lock.

10.5 Statistical analysis

10.5.1 Primary analysis

NEDA will be defined as no protocol defined disease activity events during follow-up, as specified in section 2.2. The proportion of NEDA after 96 weeks in the HSCT group and the alemtuzumab group will be compared using a univariable logistic regression model, conducted as an ITT analysis. The proportion of NEDA in each treatment arm with corresponding 95% confidence intervals (CI), the p-value for the difference in proportions and the odds ratio (OR) and 95% confidence interval (CI) for NEDA according to treatment with HSCT compared to alemtuzumab will be presented. If the odds of NEDA in the HSCT group is signicantly higher compared to the odds of NEDA in the alemtuzumab group in this model, it will be concluded that HSCT has demonstrated a superior effect on NEDA compared to alemtuzumab. The statistical test used will be based on a two-sided hypothesis. Patients lost to follow-up will be excluded from the analysis of primary outcome.

To assess the robustness of the ITT analysis, two sensitivity analyses will be conducted. First, the analysis above will be repeated in the PP population to evaluate the influence of protocol violations. Secondly, if there is imbalance in any of the stratification variables in the treatment arms, these covariates will be include in separate multivariable logistic regression models as independent variables to evaluate the influence of these on the results.

10.5.2 Secondary analyses

The secondary efficacy endpoints will be tested in a hierarchal order, corresponding to the order listed below, to account for multiple comparisons. The secondary endpoints will only be tested and interpreted as confirmatory if the primary efficacy endpoint reach a significance level of 0.05. Further, subsequent secondary endpoints will only be tested and interpreted as confirmatory if the endpoint listed ahead reaches a significance level of 0.05. Otherwise, the endpoints will be interpreted as non-confirmatory (i.e. descriptive only) independent of the p-values. The statistical tests for all secondary endpoints will be based on two-sided hypotheses. Patients lost to follow-up will be excluded from all analyses except for endpoints defined by time to event (10.5.2.2**,** 10.5.2.9, and 10.5.2.10). For these endpoints, the patients lost to follow-up up will be included in the analysis and censored at time of last visit.

10.5.2.1 Annualized rate of protocol-defined relapses (ARR) at week 96

The number of protocol-defined relapses in each treatment arm will be counted, and divided on the total time at risk in the study to estimate the ARR. Patients will contribute to time at risk from baseline to end of follow-up or withdrawal from the study, whichever occur first. The ARR in the two treatment arms will be compared using a negative binomial regression model, conducted as an ITT analysis. The ARR for each treatment arm with corresponding 95% CIs, the rate ratio with corresponding 95% CIs and p-value will be presented. The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.2.2 Time to onset of first protocol-defined relapse

Time to first protocol-defined relapse after HSCT or alemtuzumab will be compared using a Kaplan-Meier plot and an univariable Cox proportional hazards regression model, conducted as a ITT analysis. The median time to first relapse with 95% CIs, the overall hazard ratio with corresponding 95% CIs and p-values will be presented. The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.2.3 Cumulative combined unique activity (CUA) at week 96

Combined unique activity will be defined as the presence of Gd-enhancing T_1-lesions or new T_2-lesions. Cumulative CUA will be defined as the total number of new Gd-enhancing T_1-lesions and new T_2-lesions at week 24, 48 and 96. The total number of lesions after HSCT or alemtuzumab will be compared using a negative binomial regression model, conducted as an ITT analysis. Rate ratio with corresponding 95% CIs and p-value will be presented. The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.2.4 Proportion with confirmed disability improvement (CDI) at week 96

CDI will be defined as ≥ 1-point EDSS decrease from baseline that is sustained for a minimum of 24 weeks among those with a baseline EDSS of ≥ 2. The proportion of patients with CDI in the two treatment arms will be compared using an univariable logistic regression model, conducted as an ITT analysis. The proportion of participants with CDI in each treatment arm with corresponding 95% CIs, the p-value for the difference in proportions and the OR and corresponding 95% CIs for CDI according to treatment with HSCT compared to alemtuzumab will be presented. The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.2.6 Proportion with confirmed disability progression (CDP) at week 96

CDP will be defined as as ≥ 1-point EDSS increase from baseline that is sustained for a minimum of 24 weeks. The proportion of patients with CDP in the two treatment arms will be compared using an univariable logistic regression model, conducted as an ITT analysis. The proportion of patients with CDP progression in each treatment arm with corresponding 95% CIs, the p-value for the difference in proportions and the odds rate and corresponding 95% CIs for CDP according to treatment with HSCT compared to alemtuzumab will be presented. The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.2.6 Proportion with increased T_2-lesion burden at week 96

Increased T_2-lesion burden at week 96 will be defined as the the proportion of patients with presence of new T_2-lesions at week 24, 48 or 96. The proportion of patients with new T_2-lesions in the two treatment arms will be compared using an univariable logistic regression model, conducted as an ITT analysis. The proportion of participants with new T_2 lesions in each treatment arm, the p-value for the difference in proportions and the odds ratio and corresponding 95% CIs for new T_2 lesions according to treatment with HSCT compared to alemtuzumab will be presented. The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.2.7 Proportion with increased Gd-enhancing lesion burden at week 96

Increased Gd-enhancing lesion burden at week 96 will be defined as the the proportion of patients with presence of Gd-enhancing T_1-lesions at week 24, 48 or 96. The proportion of patients with Gd-enhancing lesions in the two treatment arms will be compared using an univariable logistic regression model, conducted as an ITT analysis. The proportion of participants with Gd-enhancing lesions in each treatment arm, the p-value for the difference in proportions and the odds ratio and corresponding 95% CIs for Gd-enhancing lesions according to treatment with HSCT compared to alemtuzumab will be presented. The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.2.8 Brain atrophy at week 96 compared to week 48

The difference in brain volume between week 48 and week 96 will be used to estimate the annual change in brain volume for each patient, as a measure of brain atrophy betweent two time points. Week 48 will be used as comparison instead of baseline to avoid the influence of intital pseudoatrophy related to initiation of immunomoduly treatment or HSCT. Annualized change in brain volume in the two treatment arms will be compared using a multivariable linear regression model including brain volume at week 48 as a covariate, conducted as an ITT analysis. The mean change in annualized brain volume in each treatment arm with corresponding standard deviation and the difference in mean change in annualized brain volume between the two treatment arms with corresponding 95% CIs and a p-value will be presented. The findings will also be presented as percentage change in annualized brain volume.The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.2.9 Time to first protocol-defined disease activity event

Time to first protocol-defined disease activity event after HSCT or alemtuzumab will be compared using a Kaplan-Meier plot and an univariable Cox proportional hazards regression model, conducted as a ITT analysis. The median time to first relapse with 95% CIs, the overall hazard ratio with corresponding 95% CIs and p-values will be presented. The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.2.10 Time to onset of first new T_2 lesion

Time to first new T_2 lesion after HSCT or alemtuzumab will be compared using a Kaplan-Meier plot and an univariable Cox proportional hazards regression model, conducted as a ITT analysis. The median time to first relapse with 95% CIs, the overall hazard ratio with corresponding 95% CIs and p-values will be presented. The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.2.11 Total number of Gd-enhancing lesions detected by T_1-weighted MRI at week 24, 48 and 96.

The total number of Gd-enhancing at week 96 will be calculated as the sum of lesions detected by brain MRI at week 24, 48 and 96. The total number of lesions after HSCT or alemtuzumab will be compared using a negative binomial regression model, conducted as an ITT analysis. Rate ratio with corresponding 95% CIs and p-value will be presented. The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.2.12 Proportion of patients with NEDA-4 at week 96

NEDA-4 will be defined as no protocol defined disease activity events during follow-up, as specified in section 2.2, and without a measured yearly atrophy above 0.4%. The proportion of patients with NEDA-4 in the two treatment arms will be compared using an univariable logistic regression model, conducted as an ITT analysis. The proportion of with NEDA-4 in each treatment arm with corresponding 95% CIs, the p-value for the difference in proportions and the odds ratio and corresponding 95% CIs for NEDA-4 according to treatment with HSCT compared to alemtuzumab will be presented. The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.2.13 Volumes of hyperintense lesions on T_2-weighted scans and hypointense lesions on T_1-weighed scans at week 48 and 96.

The change in volumes of T_2-lesions and T_1-lesions from week 48 to 96 will be compared in the two treatment arms using multivariable linear regression models, including lesion volume at week 48 as a covariate, conducted as a ITT analysis. The mean change in volume with corresponding 95% CIs will be presented.

10.5.2.14 Nine Hole Peg Test and Timed 25-foot walk from baseline to week 96

Each of the 9-hole peg test (9-HPT) and Timed 25-foot walk (T25FW) test will be conducted twice, and the average score for the two recordings will be converted to a Z-score. We will compare the score in the two treatment arms using a multivariable mixed effects linear regression model, conducted as an ITT analysis. The mean difference in change of T25FW and 9-HPT during follow-up between the treatment arms with corresponding CIs and p-value will be presented. The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.2.15 The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) at week 96

The change in BICAMS test score from baseline to week 96 will be estimated, and compared in the two treatment arms using linear regression, including baseline BICAMS test score as a covariate, conducted as an ITT analyses. The robustness of the ITT analysis will be tested using the two sensitivity analyses as specificed for the primary analysis.

10.5.3 Safety analyses

The safety analyses will include descriptive statistics of treatment data, laboratory data, adverse events, MRI data, withdrawal data, death data and vital signs.

10.5.4 Exploratory analyses

The following exploratory efficacy endpoints will be analyzed:

- EQ-5D-5L
- Fatigue Severity Scale (FSS)
- Multiple Sclerosis Impact Scale (MSIS) - 29
- Severity of relapses (residual disability after relapses)

In addition, exploratory subgroup analyses will be conducted of the primary and secondary efficacy endpoints within strata of sex, age at screening (<35 years vs ≥35 years), EDSS (<4 vs ≥4), disease duration (<5 years vs ≥5 years), and previous immunomodulatory treatment (< 3 drugs vs ≥3 drugs).

10.5.5 Other analyses (eg health economics, patient reported outcomes etc)

An economic evaluation will be conducted in the Norwegian part of the study comparing the interventions in arms A and B. HRQoL scores and incremental cost-effectiveness ratios (ICERs) will be calculated.

10.5.6 Descriptive statistics

Information on the following variables will be provided as descriptive statistics: Age, sex, race, time since MS diagnosis, time since first clinical event, baseline EDSS, Gd-enhancing lesions (no. and volume), T_2-lesions (no. and volume), normalized brain volume, number of relapses in past year, number of previous MS immunomodulatory treatment s, duration of previous MS immunomodulatory treatment use and generic name of previous MS immunomodulatory treatment s.

Normally distributed continuous variable will be presented as mean with standard deviation. Skewed variables will be presented as median with corresponding interquartile range (IQR). Categorical variables will be presented as frequencies and percentages.

11 STUDY MANAGEMENT

11.1 Investigator-delegation procedure

The principal investigator is responsible for making and updating a “delegation of tasks” listing all the involved co-workers and their role in the project. The PI will ensure that appropriate training relevant to the study is given to all of the relevant staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

11.2 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

11.3 Study amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Competent Authority and the Ethics Committee according to EU and national regulations.

11.4 Audits and inspections

Authorized representatives of a Competent Authority and Ethics Committee may visit the site to perform inspections, including source data verification. Likewise the representatives from sponsor may visit the site to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

12 ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted in accordance with the protocol, with the latest version of the Declaration of Helsinki, with ICH-GCP E6(R1) and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

12.1 Ethics committee approval

The study protocol, including the patient information and informed consent form to be used, must be approved by the regional ethics committee before enrolment of any patients into the study.

The investigator is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

12.2 Other regulatory approvals

The protocol will be submitted and approved by the applicable competent authorities before commencement of the study.

The protocol will also be registered in www.clinicaltrials.gov before inclusion of the first patient.

12.3 Informed consent procedure

The investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, possible risk and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent.

A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator Site File binder and also scanned to be part of the patient's electronic medical record at the hospital.

12.4 Subject identification

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient's date of birth and personal number, full names and last known addresses.

The patients will be identified in the eCRFs by patient number, initials and date of birth (not applicable for the Netherlands).

13 TRIAL SPONSORSHIP AND FINANCING

The study is sponsored by Helse Bergen HF, Haukeland University Hospital in Bergen, Norway, with funds from the Clinical therapy research in the specialist health services (Klinbeforsk). The funds are assigned the Clinic of Neurology at Haukeland University Hospital.

14 TRIAL INSURANCE

Patients will be covered by the hospital's insurance in accordance with requirements of the law in the different countries.

15 PUBLICATION POLICY

Upon study completion and finalization of the study report the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results.

The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and national regulations.

Personnel who have contributed significantly in study planning, study performance and interpretation of study results may be included by the PMC in the list of authors (ref. Vancouver convention 1988).

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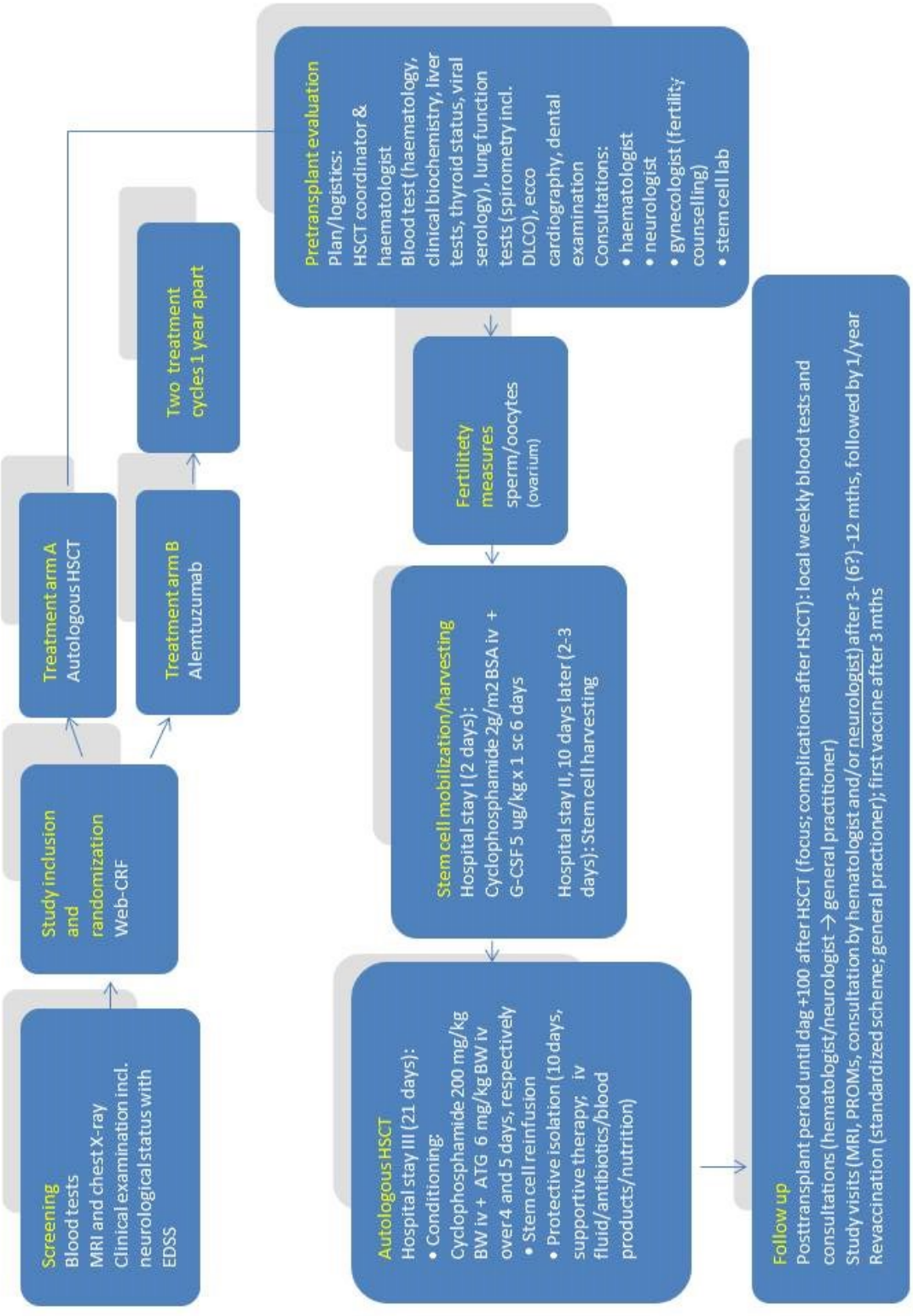
17 LIST OF APPENDICES

APPENDIX A – Patient Flow



APPENDIX B – Vaccination programme

RECOMMENDED VACCINATION PROGRAMME after autologous stem cell transplantation (HSCT) in the RAM-MS study

Vaccines	Time after HSCT				
Combination vaccine: tetanus, diphteria, pertussis, inactivated polio virus with or without *Hemophilus influenza B* and/or Hepatitis B virus components	All	6 mths	7 mths	12 mths	
Influenza virus (seasonal vaccine)	All	At 4-6 mths, followed by annual vaccination			
Pneumococcus *(Prevenar 13® or corresponding vaccine)*	All	3 mths	4 mths	5 mths	
Pneumococcus (Pneumovax® or corresponding vaccine)					12 mths
Human papilloma virus (HPV)	Women according to EBMT* and National vaccine programmes; 3 doses starting 6-12 mths after HSCT				
Supplementary vaccines (only if indicated):					
Measles, mumps and red pox (MMR) (note: live vaccine)	Individual indication	After 24 mths if seronegativity against measles and no ongoing immunosuppressive medication			
Chicken pox (varicella) (note: live vaccine)	Individual indication	After 24 mths if seronegativity against varicella and no ongoing immunosuppressive medication			
Hepatitis B	Individual indication	After 6 mths if increased risk of infection (work/travel)			
Hepatitis A	Individual indication	For travelers to certain countries, and for people at high risk of infection			

* EBMT: European Society for Blood and Marrow Transplantation

APPENDIX C – Expanded disability status scale (EDSS)

Neurological Assessment. Kurtzke Expanded Disability Status Scale (EDSS)

0	Normal neurological exam (all grade 0 in FS*)
1,0	No disability; minimal signs in one FS* (i.e., grade 1)
1,5	No disability; minimal signs in more than one FS* (more than one FS grade 1)
2,0	Minimal disability in one FS (one FS grade 2, others 0 or 1)
2,5	Minimal disability in two FS (two FS grade 2, others 0 or 1)
3,0	Moderate disability in one FS (one FS grade 3, others 0 or 1); or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory
3,5	Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 2 (others 0 or 1)
4,0	Fully ambulatory without aid, self-sufficient, up and about 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters
4,5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grad 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters
5,0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g. to work a full day without special provisions); (Usual FS equivalents are one FS grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)
5,5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for step 4,0)
6,0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than one FS grade 3+)
6,5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+)
7,0	Unable to walk beyond approx. five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grad 4+; very rarely pyramidal grade 5 alone)
7,5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grad 4+)
8,0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems)
8,5	Essentially restricted to bed much of day, has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations generally 4+ in several systems)
9,0	Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+)
9,5	Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+)
10	Death due to MS

Note 1: EDSS steps 1,0 to 4,5 refer to patients who are fully ambulatory, and the precise step number is defined by the Functional System score(s). EDSS steps 5,0 to 9,5 are defined by the impairment to ambulation, and usual equivalents in Functional System scores are provided.

Note 2: EDSS should not change by 1,0 step unless there is a change in the same direction of at least one step in at least one FS

*Excludes mental function grade 1

APPENDIX D - Patient Reported Outcomes

D.1 EQ-5D-5L

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

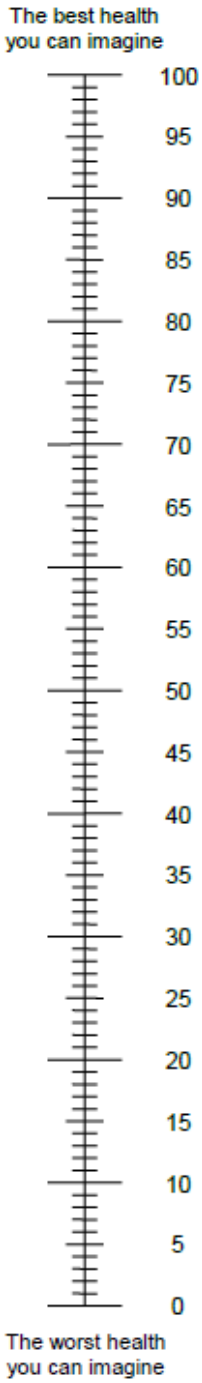
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

D.2 Fatigue Severity Scale

Fatigue Severity Scale Questionnaire

Instructions: Circle the number that best represents your response to each question.
Scoring range: 1=strongly disagree with the statement to 7=strongly agree with the statement.

During the past week, I have found that:	Score						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

FSS Scoring: Add up the circled numbers and divide by 9. _____

Compare results with the following scores:
People who do not experience fatigue score about 2.8
People with Lupus score about 4.6
People with Lyme Disease score about 4.8
People with fatigue related to Multiple Sclerosis score about 5.1
People with Chronic Fatigue Syndrome score about 6.1

D.3 Multiple Sclerosis Impact Scale (MSIS)

Multiple Sclerosis Impact Scale (MSIS-29)

- The following questions ask for your views about the impact of MS on your day-to-day life **during the past two weeks**
- For each statement, please **circle** the **one** number that **best** describes your situation
- Please answer **all** questions

In the past two weeks, how much has your MS limited your ability to...		Not at all	A little	Moderately	Quite a bit	Extremely
1.	**Do physically demanding tasks?**	1	2	3	4	5
2.	**Grip things tightly (e.g. turning on taps)?**	1	2	3	4	5
3.	**Carry things?**	1	2	3	4	5

In the past two weeks, how much have you been bothered by...		Not at all	A little	Moderately	Quite a bit	Extremely
4.	**Problems with your balance?**	1	2	3	4	5
5.	**Difficulties moving about indoors?**	1	2	3	4	5
6.	**Being clumsy?**	1	2	3	4	5
7.	**Stiffness?**	1	2	3	4	5
8.	**Heavy arms and/or legs?**	1	2	3	4	5
9.	**Tremor of your arms or legs?**	1	2	3	4	5
10.	**Spasms in your limbs?**	1	2	3	4	5
11.	**Your body not doing what you want it to do?**	1	2	3	4	5
12.	**Having to depend on others to do things for you?**	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page

In the past two weeks, how much have you been bothered by...		Not at all	A little	Moderately	Quite a bit	Extremely
13.	Limitations in your social and leisure activities at home?	1	2	3	4	5
14.	Being stuck at home more than you would like to be?	1	2	3	4	5
15.	Difficulties using your hands in everyday tasks?	1	2	3	4	5
16.	Having to cut down the amount of time you spent on work or other daily activities?	1	2	3	4	5
17.	Problems using transport (e.g. car, bus, train, taxi, etc.)?	1	2	3	4	5
18.	Taking longer to do things?	1	2	3	4	5
19.	Difficulty doing things spontaneously (e.g. going out on the spur of the moment)?	1	2	3	4	5
20.	Needing to go to the toilet urgently?	1	2	3	4	5
21.	Feeling unwell?	1	2	3	4	5
22.	Problems sleeping?	1	2	3	4	5
23.	Feeling mentally fatigued?	1	2	3	4	5
24.	Worries related to your MS?	1	2	3	4	5
25.	Feeling anxious or tense?	1	2	3	4	5
26.	Feeling irritable, impatient, or short tempered?	1	2	3	4	5
27.	Problems concentrating?	1	2	3	4	5
28	Lack of confidence?	1	2	3	4	5
29.	Feeling depressed?	1	2	3	4	5

Please check that you have circled ONE number for EACH question

APPENDIX E - Karnofsky Performance Status

Karnofsky scale	Performance Status
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalisation is indicated, although death not imminent
20	Very sick; hospitalisation necessary; active support treatment is necessary
10	Moribund; fatal processes
0	Dead

APPENDIX F - Timed 25 Foot Walk

RECORD FORMS FOR THE
MULTIPLE SCLEROSIS FUNCTIONAL COMPOSITE

LOWER EXTREMITY FUNCTION: TIMED 25-FOOT WALK

Subject ID Number | Subject Initials | Visit Date: Day / Month / Year

TIMED 25-FOOT WALK

Did patient wear an AFO? ☐ Yes ☐ No

Was assistive device used? ☐ Yes ☐ No

Assistive device used *(mark one)*:

☐ Unilateral Assistance ☐ Cane ☐ Crutch

☐ Bilateral Assistance ☐ Cane ☐ Crutch ☐ Walker/Rollator

Trial 1

Time for 25-Foot Walk ☐☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed *(mark one)*: Specify:

☐ Unable to complete trial due to physical limitations ➡

☐ Other ➡

Trial 2

Time for 25-Foot Walk ☐☐☐☐ ☐ seconds

For a complete trial, record any circumstances that affected the patient's performance:

If trial was not completed *(mark one)*: Specify:

☐ Unable to complete trial due to physical limitations ➡

☐ Other ➡

Did it take more than two attempts to get two successful trials? ☐ Yes ☐ No

If yes, please specify reasons(s) for more than two attempted trials:

APPENDIX G - Nine-Hole-Peg Test

UPPER EXTREMITY FUNCTION: NINE-HOLE PEG TEST (9-HPT)

Subject ID Number | Subject Initials | Visit Date: Day | Month | Year

9-HOLE PEG TEST

DOMINANT HAND *(Check one):* Right ☐ Left ☐

DOMINANT HAND	NON-DOMINANT HAND
Trial 1	**Trial 1**
☐☐☐ ☐ seconds	☐☐☐ ☐ seconds
For a complete trial, record any circumstances that affected the patient's performance:	For a complete trial, record any circumstances that affected the patient's performance:
If trial was not completed *(mark one):*	If trial was not completed *(mark one):*
☐ Unable to complete trial due to physical limitations ➡ Specify:	☐ Unable to complete trial due to physical limitations ➡ Specify:
☐ Other ➡	☐ Other ➡
Trial 2	**Trial 2**
☐☐☐ ☐ seconds	☐☐☐ ☐ seconds
For a complete trial, record any circumstances that affected the patient's performance:	For a complete trial, record any circumstances that affected the patient's performance:
If trial was not completed *(mark one):*	If trial was not completed *(mark one):*
☐ Unable to complete trial due to physical limitations ➡ Specify:	☐ Unable to complete trial due to physical limitations ➡ Specify:
☐ Other ➡	☐ Other ➡
Did it take more than two attempts to get two sucessful trials? ☐ Yes ☐ No If Yes, please specify reason(s) for more than two attempted trials:	Did it take more than two attempts to get two sucessful trials? ☐ Yes ☐ No If Yes, please specify reason(s) for more than two attempted trials:

APPENDIX H - The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

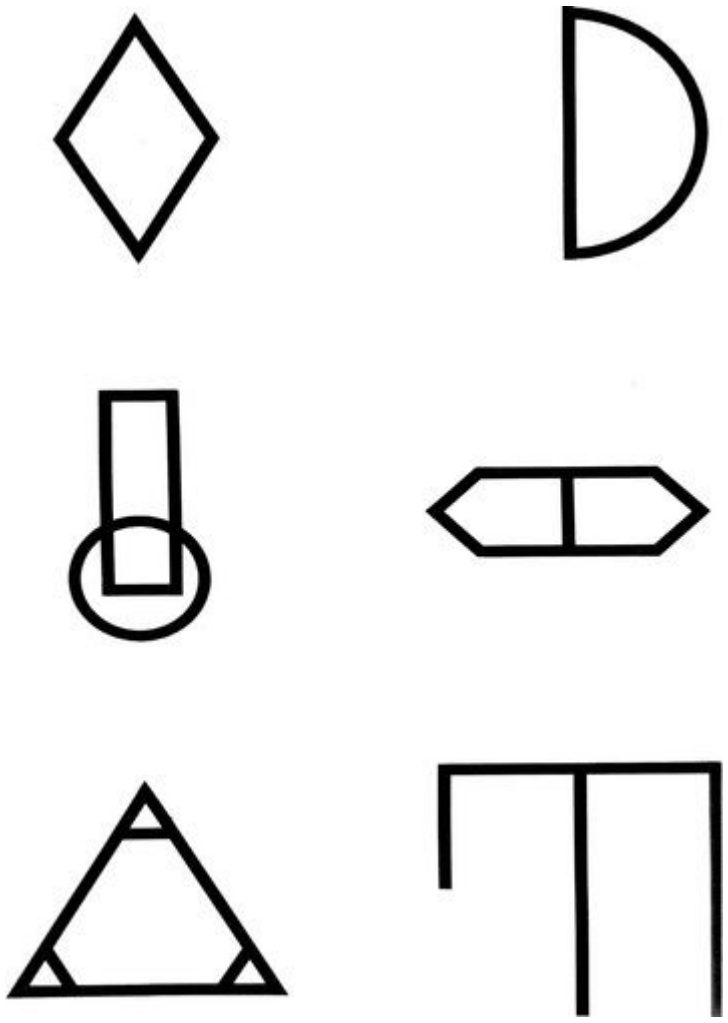
Symbol Digit Modalities test (SDMT)

California Verbal Learning Test 2. Edition (CVLT-II)

	Trial 1 Recall	Trial 2 Recall	Trial 3 Recall	Trial 4 Recall	Trial 5 Recall
football					
notebook					
island					
billiards					
paper					
river					
tennis					
cake					
folder					
boxing					
mountain					
pie					
candy					
envelope					
valley					
ice cream					
	__/16	__/16	__/16	__/16	__/16

Total Learning ___/80]

Brief Visuopatial Memory Test (BVMT-R, 1-3) - Faux Stimuli



Brief Visiopatial Memory Test – revised (BMVT-R, 1-3) Form 1

T-1	

Brief Visiopatial Memory Test – revised (BMVT-R, 1-3) Form 2

T-2	

Brief Visiopatial Memory Test – revised (BMVT-R, 1-3) Form 3

T-3	

California Verbal Learning Test 2. Edition (CVLT-II)

	Trial 1 Recall	Trial 2 Recall	Trial 3 Recall	Trial 4 Recall	Trial 5 Recall
football					
notebook					
island					
billiards					
paper					
river					
tennis					
cake					
folder					
boxing					
mountain					
pie					
candy					
envelope					
valley					
ice cream					
	__/16	__/16	__/16	__/16	__/16

Total Learning ___/80]

18 DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		2.0
Date of CTP revision		10-Jul-2017
EudraCT number		2017-001362-25
Trial number		-
Investigational Product(s)		-
Title of protocol		Randomized Autologous heMatopoietic stem cell transplantation versus Alemtuzumab for patients with relapsing remitting Multiple Sclerosis
To be implemented only after approval of the IRB / IEC / Competent Authorities		NA
To be implemented immediately in order to eliminate hazard – **IRB / IEC / Competent Authority to be notified of change with request for approval**		NA
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		NA
Section to be changed		Version 1.0 of the study protocol is re-written using a new template (NORCRIN) to ensure all requirements are met with regards to guidelines and quality.
Description of change		Substantial changes. Please refer to the document.
Rationale for change		Compliance and quality.

Number of global amendment		3.0
Date of CTP revision		22-Aug-2017
EudraCT number		2017-001362-25
Trial number		-
Investigational Product(s)		-

Title of protocol		Randomized Autologous heMatopoietic stem cell transplantation versus Alemtuzumab for patients with relapsing remitting Multiple Sclerosis
To be implemented only after approval of the IRB / IEC / Competent Authorities		NA
To be implemented immediately in order to eliminate hazard – **IRB / IEC / Competent Authority to be notified of change with request for approval**		NA
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		NA
Section to be changed		• Flow chart • Section 1.5 Benefit-risk assessment • Section 4.2 In/ex criteria • 5.2.1 Selection of doses • 5.2.2 HSCT regimen • 5.5.1 Restricted therapy • 6.1.4 Treatment and follow-up • 7.2.4 Safety laboratory parameters
Description of change		• Flow chart – correction made • Section 1.5 Benefit-risk assessment – description added • Section 4.2 In/ex criteria – correction made • 5.2.1 Selection of doses – clarifications added • 5.2.2 HSCT regimen – clarifications added • 5.5.1 Restricted therapy – clarifications re. use of CYP450 inducing agents in arm A added. • 6.1.4 Treatment and follow-up – clarifications re. preganancy testing in both study arm added. 7.2.4 Safety laboratory parameters - clarifications re. preganancy testing in both study arm added.
Rationale for change		Changes requested by NOMA after initial application submitted.

Number of global amendment		4.0
Date of CTP revision		30-Nov-2017
EudraCT number		2017-001362-25
Trial number		-
Investigational Product(s)		-

Title of protocol		Randomized Autologous heMatopoietic stem cell transplantation versus Alemtuzumab for patients with relapsing remitting Multiple Sclerosis
To be implemented only after approval of the IRB / IEC / Competent Authorities		NA
To be implemented immediately in order to eliminate hazard – **IRB / IEC / Competent Authority to be notified of change with request for approval**		NA
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		NA
Section to be changed		• Flow chart • Section 2 Study objective • Section 3 Study design • Section 4.2 and 4.3 In/ex criteria • Section 5.2.2 HSCT regimen • Section 5.2.3 Alemtuzumab – safety monitoring and emergency procedures • Section 5.5.2 Rescue medication, emergency procedures,.. • Section 6.1.4 Treatment and follow-up – Switch to other therapy • Section 6.1.8 Switch to other therapy • Section 7.1 Assessment of efficacy • Section 7.2 Assessment fo safety and tolerability • Section 7.3 Research assessments • Section 8.5.3 Exemption to SAE reporting • Section 10.5 • Section 12 Ethical and regulatory requirements

Description of change		• Flow chart – minor adjustments and corrections • Section 2 Study objective – clarifications • Section 3 Study design – clarifications • Section 4.2 and 4.3 In/ex criteria – clarification in inclusion criteria #5. Exclusion criteria #4 added on request from MPA, other minor corrections/clarifications. • Section 5.2.2 HSCT regimen – minor clarifications made on request from MPA. • Section 5.2.3 Alemtuzumab – clarification regarding safety monitoring and emergency procedures added on request from MPA. • Section 5.5.2 Rescue medication, emergency procedures,.. – clarifications added to increase patients safety and at the same time ensure data quality. • Section 6.1.4 Treatment and follow-up – Switch to other therapy – details regading daily bloodsampling for safety monitoring after stem cell reinfusion, and a statement concerning long-term follow up in case the planned extension period is not done, added on request from MPA. • Section 6.1.8 Switch to other therapy – clarification added. • Section 7.1 Assessment of efficacy – clarification added • Section 7.2 Assessment of safety and tolerability – weekly monitoring of EBV and CMV added, and pre-transplant tolerability investigations in arm A added in 7.2.7 • Section 7.3 Research assessments – clarifications and details added in section 7.3.1 for biobanking, details regarding MRI and proteomics are added. • Section 8.5.3 Exemption to SAE reporting – it is added a statement to emphasize that fatal and life-threatening SAEs are NOT exempted from expedited reporting, on request from MPA. • Section 10.5 – clarifications re. two-sided hypothesis and sensitivity analysis added on request from MPA. • Section 12 Ethical and regulatory requirements – paragraph rephrased to include compliance with the protocol, on request from MPA.
Rationale for change		Most changes requested by MPA (Swedish Medicines Agency)

Number of global amendment		4.1
Date of CTP revision		08-Dec-2017
EudraCT number		2017-001362-25
Trial number		-
Investigational Product(s)		-
Title of protocol		Randomized Autologous heMatopoietic stem cell transplantation versus Alemtuzumab for patients with relapsing remitting Multiple Sclerosis

To be implemented only after approval of the IRB / IEC / Competent Authorities		NA
To be implemented immediately in order to eliminate hazard – **IRB / IEC / Competent Authority to be notified of change with request for approval**		NA
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		NA
Section to be changed		• Section 2.2 Primary endpoint – a correction made to the definition for MS relapse • Section 4.2 Exclusion criteria – correction made to criteria #24. • Section 7.3.4 Fertility measures – minor correction with regards to which parameters will be investigated. •
Description of change		Minor non-substantial changes.
Rationale for change		To avoid misunderstandings and avoid inconsistencies in the protocol.

Number of global amendment		4.2
Date of CTP revision		20-Dec-2017
EudraCT number		2017-001362-25
BI Trial number		-
BI Investigational Product(s)		-
Title of protocol		Randomized Autologous heMatopoietic stem cell transplantation versus Alemtuzumab for patients with relapsing remitting Multiple Sclerosis
To be implemented only after approval of the IRB / IEC / Competent Authorities		NO
To be implemented immediately in order to eliminate hazard – **IRB / IEC / Competent Authority to be notified of change with request for approval**		NO

Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		YES
Section to be changed		• Flow chart
Description of change		• Flow chart – Visit 5 in Arm B is moved from 3 months to 4 months after start of treatment (V4.1) to correspond with V5 in arm A (HSCT Day +100). • Flow chart – SHBG added in footnote to list of hormones to be analysed for fertility status.
Rationale for change		Change made to V5 in arm B to align timing of sampling/assessements with Arm B.