package insert, the investigational plan, the investigator's brochure, the protocol, or the informed consent document.

6.4.11 Grading of adverse event

Toxicity grades are assigned by the study site to indicate the severity of adverse events occurring in study participants. The principal investigator (PI) has adopted the use of the National Cancer Institute's manual *Common Terminology Criteria for Adverse Events v3.0* (CTCAE; published June 10, 2003) for application in adverse event reporting. The purpose of using the CTCAE system is to provide a standard language to describe toxicities, to facilitate tabulation and analysis of the data, and to facilitate the assessment of the clinical significance of all adverse events. The CTCAE provides the following grades and descriptions in the CTCAE manual (v3.0). Adverse events should be recorded and graded 1 to 5 according to the CTCAE grades provided below:

Grade 1 = Mild adverse event

Grade 2 = Moderate adverse event

Grade 3 = Severe and undesirable adverse event

Grade 4 = Life-threatening or disabling adverse event

Grade 5 = Death

Note: In contrast to the CTCAE guidelines provided the National Cancer Institute's *Common Terminology Criteria for Adverse Events v3.0* (published June 10, 2003) all adverse events are to be reported and graded whether or not they are related to disease progression or treatment.

6.4.12 Relationship to study treatment

The relationship or attribution between an adverse event and an investigational product is determined by the site investigator and recorded on the appropriate case report form and/or SAE reporting form. The Common Terminology Criteria for Adverse Events (CTCAE) provides the following descriptors and definitions (one category classified as unrelated [Code 1] and 4 categories classified as related [Codes 2-5]) for assigning an attribution to each adverse event (for most recent update of terminology see http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

The investigator's determination of drug-relatedness (attribution) for each adverse event should be recorded in the source documentation.

6.4.13 Serious adverse event reporting

The following process for reporting a serious adverse event will ensure appropriate compliance with the ICH guidelines (http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html).

Serious adverse event identification and determination of reporting timeline:

When an investigator identifies a serious adverse event (as defined above), he or she must notify the principal investigator, the IRB, and Genzyme pharmacovigilance. In addition to telephone reporting, these events must be entered on the Serious Adverse Event Form (MedWatch).

6.4.14 Study drug discontinuation

At the initial clinic visit, study patients will be made aware of potential side effects of alemtuzumab. At each patient visit, patients will be inquired about any of these side effects. Should it be felt by the patient and the examining physician that these side effects warrant discontinuation of study drug, the offending therapeutic intervention will be terminated.

6.4.15 Pregnancy (SAE reporting requirements)

Any pregnancy that occurs during a clinical study with an investigational drug must be reported as an SAE for tracking purposes only. All pregnancies that are identified during this study need to be followed to conclusion and the outcome reported. Female participants should immediately inform the investigator of pregnancies and future treatment options should be discussed.

The site investigator should report all pregnancies within 24 hours (as described above in SAE Reporting) using the SAE form. The site investigator should counsel the participant and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy, and a follow-up SAE reporting form should be submitted detailing the outcome.

6.4.16 Study completion and post-study treatment

Outside the scope of this study, the intention is to follow all study participants in participating centers long-term, and to record disease activity and treatment response.

6.4.17 Role of key site personnel

The treating physician and other designated qualified personnel will see the participant. The physician will perform all neurological and non-neurological assessments, and will have access to laboratory results.

6.4.18 Statement of compliance

This trial will be conducted in compliance with the protocol, current Good Clinical Practice (GCP), adopting the principles of the Declaration of Helsinki, and all applicable regulatory requirements.

Before study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate ethics review committee or Institutional Review Board (IRB). Any amendments to the protocol or consent materials must also be approved before they are implemented.

7.2 Screening

This research study will be explained in lay language to each potential research participant. The participant will sign an informed consent form before undergoing any screening study procedures. If the inclusion criteria are met at the screening visit, the participants will be enrolled in study. Each participant will be assigned a unique study ID.

7.3 Patient demographics and baseline characteristics

Each selected study site has a large population representing diverse age, backgrounds, and ethnicity. This study will enroll all patients that meet the inclusion criteria.

7.4 Treatment exposure and compliance

The participant will receive treatment at study visits 3 and 7

Because study drug is administered IV in the presence of research team members, participant will be 100% compliant.

7.5 Efficacy

Efficacy will be assessed by clinical evaluation and MRI scanning. Clinical evaluation includes neurological examination, and EDSS assessment. Brain MRI will assess T1 lesion load, T2 number and lesion load, number of Gd^{+} lesions.

7.5.1 Definition of a relapse

A clinical relapse is defined as new neurologic symptoms, lasting at least 24 hours, is associated with an increase in the EDSS by ≥ 0.5 points, and consistent with new demyelination. Two relapses must be separated by at least 30 days. Due diligence to rule out pseudoexacerbations will be up to the PI in each individual case.

7.5.2 EDSS

A standard EDSS will be performed at certain study visits (screening or baseline, 6 months , 12 months, and any relapse visits). This will include both a composite score and subsection score, recorded on a CRF. The EDSS is a scale providing a disability score (0 to 10) based on neurological examination and information about how the patient is able to perform tasks such as long walking. The EDSS may be conducted by a different doctor than the one the patient typically sees for treatment of MS. In order to make sure that this EDSS doctor is as objective as possible, the patient should not explain to this doctor how he/she is feeling that particular day, what symptoms may be bothersome at that time, or what treatment the patient is currently receiving for MS (see Appendix 2.

7 Visit schedule and assessments

7.1 Study outline

Visit	1	2	3	4	5	6	7	8	9
Month	Screening -1	Baseline -15	0 - 0.5	3	6	9	12	18	24
Inclusion/exclusion	x	x							
Demographic information	x								
Informed consent	x								
Medical history	x								
Concomitant meds	x	x		x	x	x	x	x	x
Physical exam	x			x		x			x
Vitals	x			x	x	x	x	x	x
EDSS	x				x		x		x
Alemtuzumab treatment (5 consecutive days, 12 mg/d)			x				x		
Columbia Suicide Severity Rating Scale	x			x	x	x	x	x	x
QoL	x				x		x		x
Neurological examination	x			x	x	x	x		x
Blood draw for mechanistic studies	x			x	x	x	x		x
Laboratory assessments for safety monitoring*	x	x							
Pregnancy test		x							
OCT	x				x		x		x
Visual acuity	x				x		x		x
MRI	x				x		x		x
Adverse events	x	x		x	x	x	x	x	x

**Laboratory assessments for safety monitoring will be drawn monthly for until 48 months after the last dose of alemtuzumab as per REM. These laboratory assessments include a CBC with differential, a serum creatinine, and urine analyses with cell count. A thyroid function test such as a TSH will be obtained at baseline, and every 3 months thereafter.*

7.5.3 MRI

All imaging data at UT Southwestern will be acquired on single 1.5 or 3 Tesla MRI unit within the Advanced Imaging Research Center (AIRC), located in the Bill and Rita Clements Advanced Medical Imaging Building within UT Southwestern Medical Center campus. Study participants at the Dallas VA. the Multiple Sclerosis Treatment Center of Dallas, and the Neurology Center of San Antonio will be scanned on similar scanners at their sites, using compatible software sequences. All imaging data will be analyzed at the AIRC. The AIRC, in partnership with other North Texas institutions, aims to further research in magnetic resonance imaging and translation of discoveries into clinical practice.

7.5.4 Standard MRI protocol performed at all sites

Standardized MRI studies of the brain will be performed at weeks 0 and 96. Clinical imaging studies of the brain and/or spinal cord performed during or immediately following the onset of a clinical exacerbation will be performed at the discretion of the site PI with scan costs covered under the medical standard of care. A clinical MRI of the cervical spinal cord with and without contrast will be recommended to study participants at week 0 and week 96 as medical standard of care. The MS specialist with neuro-imaging expertise will be responsible for ensuring that a uniform protocol ("Dummy scans") is implemented at specified sites for the collection of uniform, multi-center data for post processing. In addition, this specialist will evaluate all MRI studies of the CNS for interval change (i.e. new and enlarging T2 lesion(s), gadolinium enhancement) during follow-up imaging studies and imaging studies acquired during clinical events. At Year 2, changes in T2-lesion volumes, and brain atrophy (SIENA) will be determined.

Standard imaging protocol:

1. Scout/Localizers

   Routine T1-weighted axial, coronal, and sagittal scout images will be acquired to assess the field of view and head positioning.

2. 3D T2-Weighted Images

   A 3D T2-weighted imaging sequence will be performed to allow for a proper assessment of infratentorial lesions.

   - 1.0 x 1.0 x 1.0 mm^3, TE/TR/TI=229/2500/1600, flip angle 90 degrees, 250 x 250 x 180 FOV, NEX=1, 164 slices, 4:33 duration

3. 3D Pre-Contrast T1-Weighted Volumetric Gradient Echo Images

   A 3D pre-contrast T1-weighted volumetric gradient echo sequence will be performed (anticipated acquisition time: 4-5 minutes) for future volumetric