STATISTICAL ANALYSIS PLAN

ALK8700-A301/NCT02634307

Study Title:	A Phase 3 Open Label Study to Evaluate the Long-term Safety and Tolerability of ALKS 8700 in Adults with Relapsing Remitting Multiple Sclerosis
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APPROVAL

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VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
Version 1.0	14 Dec 2016	Final
Version 2.0	15 Apr 2021	SAP amendment for COVID-19 impact etc.

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ABBREVIATIONS

The following abbreviations are used in the statistical analysis plan.

Abbreviation or Term	Explanation or Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
ARR	Annualized Relapse Rate
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical [Classification System]
AUC_{last}	Area Under the plasma Concentration versus time curve calculated using the trapezoidal method from time zero to the last observed concentration above the lower limit of quantification.
C_{max}	Maximum Observed Concentration
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
DMF	Dimethyl Fumarate
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
EQ-5D-5L	Euroqol Group Health Outcome Measure (5-Level)
ET	Early Termination
FAS	Full Analysis Set
FS	Functional System
GCP	Good Clinical Practice
GdE	Gadolinium-Enhancing
GI	Gastrointestinal
LDH	Lactic Dehydrogenase
MedDRA	Medical Dictionary For Regulatory Activities

Abbreviation or Term	Explanation or Definition
MMF	Monomethyl Fumarate
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NEDA	No Evidence of Disease Activity
PCS	Potentially Clinically Significant
PDEAE	Post-discontinuation Adverse Event
PK	Pharmacokinetic
QoL	Quality of Life
QTcB	QT Interval Corrected Using Bazett's Formula
QTcF	QT Interval Corrected Using Fridericia's Formula
RRMS	Relapsing-Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SF-12	Short Form 12 Health Survey
SF-12 MCS	Short Form 12 Health Survey Mental Component Summary
SF-12 PCS	Short Form 12 Health Survey Physical Component Summary
T25-FW	Timed 25-Foot Walk
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time to Reach C_{max}
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods and data presentation to be used for analyzing and reporting safety as well as efficacy data for study ALK8700-A301. This document has been prepared based on Biogen Inc. ALK8700-A301 study protocol amendment Version 5.0 (dated 27 September 2019) [1].

1.1. Study Objectives

The objectives of this study are: 1) to evaluate the long-term safety and tolerability of ALKS 8700 (also known as BIIB098 and diroximel fumarate) for up to 96 weeks of treatment in adult subjects with RRMS and 2) to evaluate treatment effect over time in adult subjects with RRMS treated with ALKS 8700.

1.2. Summary of the Study Design

This is a multicenter open label study to evaluate the long-term safety and tolerability of ALKS 8700 administered up to 96 weeks for the treatment of RRMS. The target population for this study will be adults, aged 18 to 65 years, diagnosed with RRMS.

Subjects will enter into the study in one of two ways:

1. De Novo Subjects: Those who have not participated in any prior eligible study of ALKS 8700
2. Rollover Subjects: Those who have completed the treatment period for any prior eligible study of ALKS 8700

De Novo Subjects will be initially evaluated for eligibility at screening (Visit 1) that may last up to 21 days prior to Visit 2. For Rollover Subjects, Visit 2 will be the first visit of the study and there will not be a separate screening visit. For these subjects, Visit 2 of this study will occur at the time of or within 7 days of the subject's end of treatment visit in the antecedent study. Completed assessments taken at the end of treatment visit of the antecedent study will be carried forward and do not need to be repeated at Visit 2 of this study unless otherwise specified in the schedule of assessments Table 1. At Visit 2, all eligible, consenting subjects will begin open label treatment. Any subject not currently receiving ALKS 8700 or DMF will initiate treatment with ALKS 8700 231 mg twice daily on Day 1 through Day 7 followed by 462 mg twice daily from Day 8 onwards. For those subjects already receiving ALKS 8700 or DMF prior to Day 1, the initial ALKS 8700 dose will be 462 mg twice daily starting from Day 1.

Study drug includes ALKS 8700 231 mg administered as one capsule and ALKS 8700 462 mg administered as two, 231 mg capsules. Capsules will be administered orally, twice per day. Study staff will administer the first dose of ALKS 8700 at Visit 2 (Day 1). From that point on during the treatment period, the staff will dispense ALKS 8700 for subjects' self-administration. Subjects will be instructed to take study drug with or without food.

Starting on Day 8 of treatment, dose reduction to ALKS 8700 231 mg twice daily is permitted at the investigator's discretion for subjects who are unable to tolerate ALKS 8700 462 mg twice daily. Once a subject has stabilized after dose reduction, attempts should again be made to

achieve and maintain the target maintenance dose of ALKS 8700 462 mg twice daily. If a subject remains unable to tolerate ALKS 8700 462 mg twice daily after 1 month on treatment (ie, by Visit 4), further dose reduction will not be permitted and the subject will be discontinued from the study.

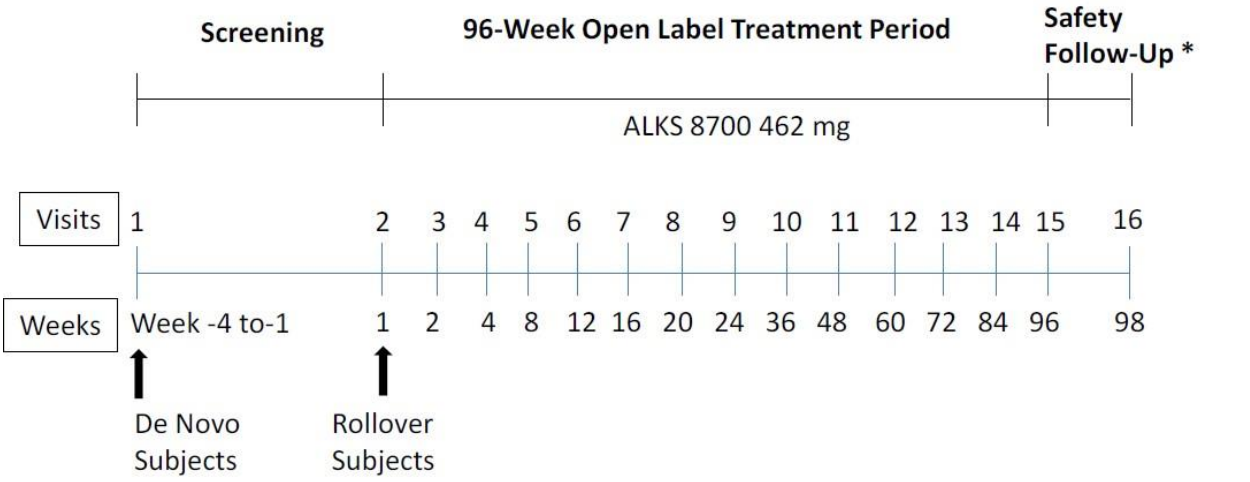
The study may be stopped at any time or study sites may be closed at the sponsor's discretion.

During the 96-week treatment period (Visits 2-15), subjects will return to the clinic for periodic scheduled visits for the assessment of safety, tolerability, pharmacokinetics (in a subset of De Novo subjects in selected sites), and clinical status. Two safety and tolerability assessments by phone will be scheduled (one between Visits 2 and 3 and one between Visits 3 and 4). See Figure 1 or a study schematic.

Subjects will return to the clinic for a safety follow up visit (Visit 16) 2 weeks after the end of treatment visit (Visit 15). Any subject who prematurely discontinues from the study will be asked to return to the clinic for an early termination (ET) visit (Visit 15) as well as a safety follow up visit 2 weeks later (Visit 16).

Subjects who complete the study or who terminate the study early and have a last measured lymphocyte count $< 0.8 \times 10^3/\mu L$ will return to the clinic for additional lymphocyte count monitoring visits every 2 months starting from Visit 16 for a period of 6 months (i.e., a maximum of 3 visits or until lymphocyte counts reach normal limits ($\geq 0.91 \times 10^3$ /μL), whichever occurs first.

Figure 1: Study Design Schematic



* Lymphocyte monitoring follow up visits (maximum 3 visits within 6 months) may be required after this visit

Table 1: Schedule of Visits and Assessments

	Screening	96-Week Open-Label Treatment[1]														
Visit	**1**[2]	**2**[3]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 /ET**	**16 Follow-up**
Day	**-21 to -1**	**1**	**15 (±3)**	**29 (±3)**	**57 (±5)**	**85 (±5)**	**113 (±5)**	**141 (±5)**	**169 (±5)**	**253 (±5)**	**337 (±5)**	**421 (±5)**	**505 (±5)**	**589 (±5)**	**673 (±5)**	**687 (±5)**
Week	**-3 to -1**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**98**
Informed Consent[4]	X															
Eligibility Criteria Review	X	X[5]														
Demographics and Medical History	X															
Physical Exam[6]	X	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[7]	X															
Weight	X	X[5]		X	X	X			X	X	X	X	X	X	X	X
Urine Pregnancy Test	X	X[5]	X	X	X	X	X	X	X	X	X	X	X	X		
Serology Testing[8]	X															
Biochemistry, Urinalysis, & Hematology Samples[9]	X	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[10]	X	X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Standard 12-Lead ECG	X	X[5]	X	X	X	X			X	X	X		X		X	X
Pharmacokinetic Sampling[11]		X[5]	X	X	X											
[redacted]																
Timed 25-Foot Walk	X	X[5]				X			X	X	X	X	X	X	X	

	Screening	96-Week Open-Label Treatment[1]														
Visit	**1**[2]	**2**[3]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15 /ET**	**16 Follow-up**
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Week	**-3 to -1**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**98**
EDSS	X	X[5]				X			X	X	X	X	X	X	X	
SF-12		X[5]							X		X		X		X	
EQ-5D-5L		X[5]							X		X		X		X	
C-SSRS[12]	X	X[3,4,5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensation		X	X	X	X	X	X	X	X	X	X	X	X	X		
Study Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	
Emergency Treatment Card[15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EDSS=Expanded Disability Status Scale; EQ-5D-5L=EuroQol Group health outcome measure 5-level version; ET=early termination; [redacted]; SF-12=12-item Short Form health survey
Note: Two safety and tolerability assessments by phone will be conducted (one between Visits 2 and 3 and one between Visits 3 and 4)

[1] Unscheduled visit may occur at any time as per protocol requirements
[2] Only De Novo Subjects will participate in the screening visit
[3] For Rollover Subjects, identical assessments taken at the last treatment visit in the antecedent study do not need to be repeated at Visit 2 in the current study
[4] Eligible, consenting De Novo Subjects will give written consent at screening. Eligible, consenting Rollover Subjects will give written consent prior to participating in any study-specific procedures at Visit 2. Written confirmation of a subject's willingness to continue in the trial will be required if one or more of the following occur during the study: MS relapse, disability progression, [redacted]

[5] To be conducted pre-dose at Visit 2

[6] Full physical exam at screening. Brief physical exam, symptom-directed, at all other visits

[7] For Rollover Subjects, height will be carried over from information recorded in the antecedent ALKS 8700 study in which they participated

[8] Serology testing includes hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus antibody

[9] 9Urinalysis includes urine dipstick, urine microscopy (as applicable), urine beta-2-microglobulin, urine albumin, and urine creatinine

[10] Vital sign measurements include temperature, respiratory rate, blood pressure, and heart rate. Blood pressure, respiratory rate, and heart rate will be measured after the subject has been in a seated or supine position for at least 5 minutes

[11] Pharmacokinetic samples will be collected in a subset of de novo subjects at selected sites. Samples will be collected pre-dose, and at 0.5, 1, 2, 3, 4, 6, and 8 hours after the morning dose on Days 1 and 29. Additional PK samples will be collected prior to and approximately 2-3 hours following the morning or evening dose on Days 15 and 57. Specifics of study visits where PK samples will be collected and PK sampling procedures will be provided to the study sites outside of this protocol.

[redacted]

[14] Use "Screening" version at screening; use "Since Last Visit" version at all other scheduled timepoints

[15] At Visit 2, dispense Emergency Treatment Card to De Novo Subjects and confirm possession/redispense if necessary for Rollover Subjects. At all other visits, confirm subject's possession of card and redispense if necessary

2. SAMPLE SIZE CONSIDERATION

A sample size of approximately 1000 patients will contribute to the long-term safety experience of ALKS 8700 in subjects with RRMS, to provide sufficient patient exposure to meet the ICH guidance on the extent of patient exposures required to assess clinical safety for a new drug.

3. DATA ANALYSES

3.1. Study Population

The study population, defined as all enrolled subjects who receive at least one dose of ALKS 8700, will be divided into three enrollment groups for summarizing safety and efficacy data:

1. De Novo Subjects
2. Rollover Subjects who were in ALKS8700 treatment group
3. Rollover Subjects who were in DMF treatment group

3.1.1. Definitions of Analysis Populations (Analysis Sets)

3.1.1.1. Safety Population

The safety analysis set, defined as all enrolled subjects who receive at least one dose of ALKS 8700, will be used in the safety analyses.

3.1.1.2. Efficacy Population

The efficacy endpoints to assess treatment effect over time will be analyzed using data from the Full Analysis Set (FAS), defined as all subjects who receive at least one dose of ALKS 8700 and have had at least one post-baseline efficacy assessment.

3.1.1.3. Pharmacokinetic Population

The PK analyses will use the PK analysis set, defined as all subject who receive at least one dose of study drug and have at least one measureable concentration of MMF. Pharmacokinetic samples will be collected in a subset of approximately fifty de novo subjects at selected sites.

3.1.1.4. Subgroup Variables

Renal impact will be defined by baseline GFR as: normal ($\geq$ 90 mL/min/1.73m^2), mild ($60 \leq$ - $<$ 90 mL/min/1.73m^2) and moderate – severe ($<$ 60 mL/min/1.73m^2).

Age subgroup will be defined as age $<$ 55 and age $\geq$ 55 at baseline.

3.1.2. Disposition

Subject disposition will be summarized by enrollment group and overall in terms of the following:

- Subjects enrolled in the study
- Subjects in the safety population
- Subjects in the FAS population
- Subjects in the Pharmacokinetic Population

- Subjects who completed the treatment period
- Subjects who completed the study (treatment and follow up period)
- Subjects who discontinued from the study during the treatment period
- Subjects by the reason for early discontinuation

Percentages of disposition are based on the subjects in the Safety Population. Reason for early discontinuation will be as indicated on the disposition electronic case report form (eCRF). A listing of disposition will be provided for all subjects.

3.1.3. Protocol Deviations

Subjects with major protocol deviations in the following categories will be summarized and listed by enrollment group and overall for each category as listed below:

- Did not meet the inclusion/exclusion criteria
- Received prohibited medications
- Non-compliant with study medication, as defined by subjects taking less than 70% or more than 105% of the protocol specified amount of study medication
- Other major protocol deviations

3.2. Demographics and Baseline Characteristics

For De Novo Subjects and Rollover Subjects who were in DMF treatment group in ALK8700 A302, demographics and baseline characteristics data will be collected at Visit 2. For Rollover Subjects who were in ALKS 8700 treatment group, these data will be carried over from information recorded in the antecedent ALK8700-A302 study unless otherwise specified.

Demographic data, including age, age category (18-19, 20-29, 30-39, 40-49, 50-55, and > 55, as well as < 40, ≥ 40), gender, race, weight, body mass index (BMI), ethnicity and region (US, non-US) will be summarized by enrollment group and overall.

Baseline disease characteristics will also be summarized by enrollment group and overall, using descriptive statistics. These include years since disease (MS) onset, years since diagnosis, number of relapses in the past 12 months, prior Disease modifying therapy, baseline Expanded Disability Status Scale (EDSS) scores and EDSS score category (0, 1-1.5, 2-2.5, 3-3.5, 4-4.5, and ≥ 5).

[redacted]

Medical history will be summarized by enrollment group and overall for the Safety Population. Demographic, baseline characteristics and medical history listings will be provided for all subjects.

3.3. Prior and Concomitant Medications

Prior medications are defined as medications taken prior to the first dose of the study medication (i.e., medications with a stop date prior to the first date of study drug in the current study). Concomitant medications are defined as medications taken during the period between the first dose date and the last dose date of study drug, inclusive. Post-discontinuation medications are defined as medications taken after the last dose of study drug. All medications as documented by the investigator will be coded using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) drug dictionary herbal enhanced version (2016, 1st quarter).

Prior and concomitant medications will be summarized by the preferred drug name for the Safety Population, by enrollment group and overall. If a subject has taken a prior or concomitant medication more than once, the subject will be counted only once for the medication. All reported medications will be presented in the subject data listing.

3.4. Treatment Adherence Rate and Extent of Exposure

Treatment adherence will be defined as: (number of capsules taken) / (number of capsules expected to be taken) * 100. When a subject discontinues treatment early, the number of capsules that should have been taken is based upon the duration the subject was on treatment.

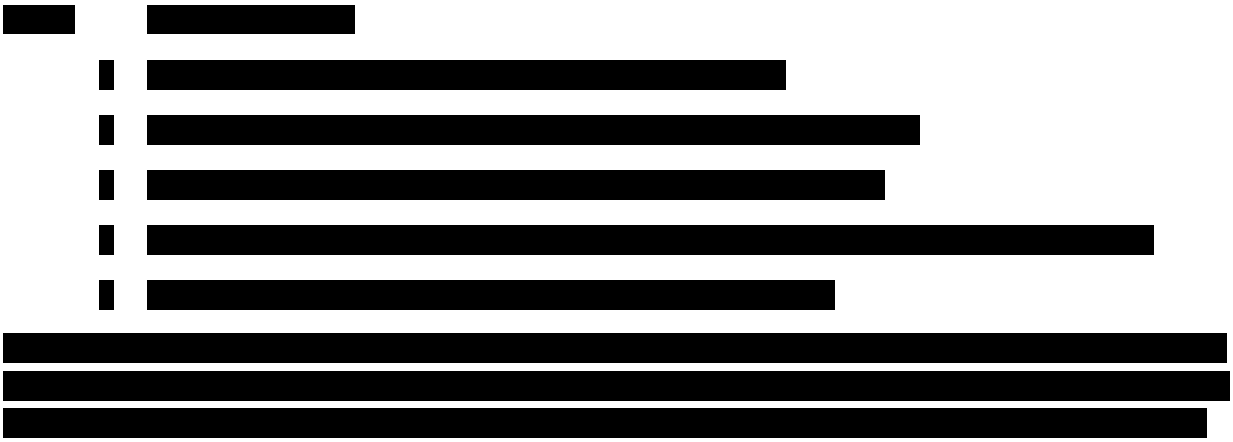
Total number of days the subject is on study drug will also be summarized as a continuous variable and categorized into 12-week intervals. Days on study drug will be calculated as the number of days from date of first dose to date of last dose plus 1.

Treatment adherence and exposure will be summarized by enrollment group and overall. Supportive listings will be provided.

3.5. Efficacy Analyses

3.5.1. General Considerations

All efficacy analyses will be carried out using the FAS population. For rollover subjects, efficacy assessment in the antecedent ALK8700-A302 study will be carried over as baseline if visit 2 in current study is not collected. All efficacy endpoints will be summarized by enrollment group and overall. Supportive listings will be provided.



[redacted]

3.5.3. Clinical endpoints

- The change from baseline in the EDSS score
- Proportion of subjects experiencing a relapse at Week 96
- Annualized Relapse Rate (ARR) at Week 96
- Time to onset of 12-week confirmed disability progression
- Change in 25-Foot Walk from Baseline
- Proportion of subjects with No Evidence of Disease Activity (NEDA) at Week 96

EDSS Score

The EDSS is used to measure and evaluate MS patients' level of functioning. The EDSS provides a total score on a scale that ranges from 0 to 10. The first levels 1.0 to 4.5 refer to people with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability. The range of main categories include (0) = normal neurologic exam; to (5) = ambulatory without aid or rest for 200 meters; disability severe enough to impair full daily activities; to (10) = death due to MS. In addition, it also provides eight subscale measurements called Functional System (FS) scores: pyramidal (motor function); cerebellar; brainstem, sensory; bowel and bladder; visual, cerebral or mental; and other. The Functional Systems (FS) are scored on a scale of 0 (low level of problems) to 5 (high level of problems) to best reflect the level of disability observed clinically. The total EDSS score is determined by two factors- gait and FS scores. EDSS scores below 4.0 are determined by the FS scores alone. EDSS scores between 4.0 and 9.5 are determined by both gait abilities and FS scores. For this study, the fatigue score should be recorded but not included in the calculation of the cerebral FS score.

The EDSS score and change from baseline during the Treatment Period will be summarized by enrollment group and overall.

Relapse

A protocol-defined relapse consists of the following:

- New or recurrent neurologic symptoms, not associated with fever or infection, lasting for at least 24 hours, accompanied by one or more of the following:
  - New objective neurological findings upon examination by the treating neurologist that are functionally consistent with findings on the EDSS (performed within

7 days of onset of symptoms) with an increase over the prior visit of ≥ 0.5 for the total score,

- An increase of ≥ 2 in one FS subscale scores and/or
- An increase of ≥ 1 in two FS subscale scores, except bladder/cognitive changes.

New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse. New or recurrent neurologic symptoms that occur less than 30 days following the onset of a protocol-defined relapse will be considered part of the same relapse, i.e., if 2 relapses have onset days that are ≤ 29 days of one another, they will be counted only as 1 relapse, and the onset date used in the analysis will be the onset date of the first relapse.

Assessment regarding protocol defined relapses will be summarized as frequency of relapses per subjects (0, 1, 2, 3, ≥ 4); along with estimated proportion of subjects experiencing a relapse at Week 96, which will be calculated with the use of the Kaplan–Meier product-limit method.

Annualized Relapse Rate

The annualized relapse rate for each enrollment group will be calculated as the total number of relapses experienced in the group divided by the total number of patient-years on study. In addition, the relapse rate for an individual patient will be calculated as the number of relapses for that patient divided by the number of patient-years followed. Based on these individual relapse rates, the mean and median for each enrollment group will be presented.

Time to Onset of 12-week Confirmed Disability Progression

The time to onset of 12-week confirmed disability progression is defined as the time from baseline to the first disability progression that is confirmed at the next regularly scheduled visit ≥ 12 weeks after the initial disability progression.

Disability progression is defined by one of the following:

- an EDSS increase of at least 1.5 points from baseline EDSS = 0
- an EDSS increase of at least a 1.0 point from baseline EDSS between 1.0 and 5.5 (inclusive), or
- an EDSS increase of at least 0.5 points from baseline EDSS = 6.0.

The date of the initial EDSS assessment at which the minimum increase in the EDSS is met will be the date of onset of the progression (tentative progression). The progression is defined as confirmed when this minimum EDSS change is present on the next study visit occurring after 12 weeks or longer from the onset of the progression. EDSS assessments within 30 days after a protocol-defined relapse will not be used for confirmation of disability progression. If a subject meets the defined criteria of confirmed progression and is also having a relapse, the subject will be required to meet the defined minimum criteria at the subsequent visit.

Death due to MS before a confirmed disability progression will be counted as progression. If the subject was in the midst of a tentative progression at the time of death (e.g. the EDSS evaluation prior to death is a tentative progression), the progression date will be the date of the onset of the progression. Otherwise, the progression date will be the date of death.

Subjects who do not have a confirmed progression based on the above rules will be censored. The censor date will be the date of the last EDSS assessment in the study, unless the subject was in the midst of a tentative progression. For subjects with a tentative progression at the last study visit, the censor date will be the date of the onset of the progression. Subjects who withdraw from the study after the baseline visit but prior to the first clinical evaluation scheduled visit will be censored at baseline.

Estimated proportion of subjects with 12-week confirmed progression at 48, 60, 72, 84, and 96 weeks will be calculated with the use of the Kaplan–Meier product-limit method and reported by enrollment group and overall.

Timed 25-foot walk (T25-FW) score

The T25-FW is a reliable quantitative mobility and leg function performance test based on a timed 25-foot walk (T25-FW). The subject is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. Subjects are allowed to use assistive devices (canes, crutches, walkers) as needed. The time is calculated from when the lead foot crosses the start point to when the subject has reached the 25-foot mark. The task is immediately administered again by having the subject walk back the same distance. The score for the T25-FW is the average of the two completed trials.

The T25-FW score and change from baseline during the Treatment Period will be summarized by enrollment group and overall.

No Evidence of Disease Activity (NEDA)

Both NEDA-3 and NEDA-4 definitions will be used to identify subjects with NEDA. The definition of NEDA-3 encompasses a combination of three related measures of disease activity: no relapses, no confirmed disability progression sustained for 12 weeks as measured on EDSS and no MRI disease activity, defined as no new GdE lesions and no new or enlarging T2 hyperintense lesions. The definition of NEDA-4 is the above definition of NEDA-3 with the addition of a mean annualized rate of brain volume loss (AR-BVL) of less than 0.4% where AR-BVL is derived from percentage brain volume change from baseline (PBVC) and is calculated as ((PBVC/100+1)^(365.25/days)–1)*100 [2].

Proportion of Subjects with NEDA-3 and NEDA-4 at Week 96 will be summarized by enrollment group and overall. Estimated proportion of subjects with NEDA-3 and NEDA-4 at week 96 will be estimated using Kaplan-Meier product-limit method and reported by enrollment group and overall.

3.5.4. Patient Reported Outcomes

The following patient reported outcomes will be summarized for each enrollment group and overall:

- The change from baseline in the Short Form 12 Health Survey (SF-12) component and summary scores through Week 96
- The changes from baseline in the EQ-5D-5L visual analog scale (VAS) scores through Week 96

Short Form 12 Health Survey (SF-12) Component Scores

Quality of life will be assessed using the 12-item Short-Form health survey Version 2 (SF 12v2) [3]. The 12-item Short Form or SF-12 is a generic quality of life (QOL) measure based on the SF-36 Health Survey. The SF-12 captures approximately 90% of the variance of the SF 36. The SF-12 provides two summary indices of health-related quality of life: the Physical Component Summary (SF-12 PCS) and the Mental Component Summary (SF-12 MCS). SF-12 PCS and SF12 MCS scores will be computed using the transformed scores of 12 questions and range from 0 to 100 (Mean=50, standard deviation [SD] =10 in the general US population), where zero indicates the lowest level of health measured by the scales and 100 indicates the highest level of health [3].

EQ-5D-5L Visual Analog Scale (VAS) Scores

The 5-level EQ-5D version (EQ-5D-5L) [4] is designed for self-completion by subjects and consists of 2 pages - the EQ-5D-5L descriptive system and the EQ visual analog scale (VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the respondent's self-rated health on a vertical, visual analog scale where the anchors are labeled 'Best imaginable health state' (score of 100) and 'Worst imaginable health state' (score of 0). The EQ-5D-5L descriptive system can be converted into a single summary EQ-5D Index [5].

The Patient Reported Outcomes scores and changes from baseline during the Treatment Period will be summarized by enrollment group and overall.

3.6. Safety Analyses

3.6.1. General Considerations

All safety analyses will be carried out using the safety analysis set (Section 3.1.1.1) and will be summarized by enrollment group and overall unless specified otherwise.

3.6.2. Adverse Events

All adverse events (AEs) will be coded by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities MedDRA version 20.1 or higher. The verbatim term will be included in the AE listings.

AEs will be identified as emerging in the treatment period and the follow up period. During the treatment period, an AE will be considered as treatment-emergent AE (TEAE) if the event starts or worsens on or after the date of first dose of study drug in the current study. The Treatment Period is defined as the first dose start date to the date of end of treatment (EOT) in the current study, inclusive.

During the follow up period, post-discontinuation emergent AEs (PDEAEs), defined as AEs that started or worsened after date of the EOT visit, will be summarized. For PDEAEs, the greatest severity before or on the date of the EOT visit will be used as the benchmark for the comparison

of the AEs occurring during the follow up period. The Follow-up Period is defined as the period between the date of the EOT visit plus 1 day and the last study visit, inclusive.

An overview table, including number of subjects with TEAEs, serious AEs (SAEs), AEs leading to study discontinuation, study drug-related TEAEs, and PDEAEs will be provided. Adverse events leading to study discontinuation and SAEs leading to death will be summarized in the period when the discontinuation or death occurred.

The following summary tables will be provided for the treatment period by enrollment group and overall:

- TEAEs by System Organ Class and Preferred Term
- TEAEs by System Organ Class, Preferred Term, and severity
- TEAEs by System Organ Class, Preferred Term, and relationship
- Study drug related TEAEs by System Organ Class and Preferred Term
- TEAEs experienced by ≥ 5% of subjects by System Organ Class and Preferred Term
- SAEs by System Organ Class and Preferred Term
- AEs leading to study discontinuation by System Organ Class and Preferred Term
- Adverse Events of Special Interest by System Organ Class and Preferred Term

In addition, an AE overview table and AEs by System Organ Class and Preferred Term for PDEAEs during the Follow-up Period will be provided.

All AE tables will be sorted by System Organ Class and then Preferred Term in decreasing frequency based on all subjects in the Safety Population.

A subject having the same AE (as determined by the coded MedDRA preferred term) more than once will be counted only once in the number and percentage of subjects calculation for that AE. Similarly, if a subject has more than one AE in a SOC, the subject will be counted only once in the total number and percentage of subjects with an AE for that SOC. If a subject has the same AE on multiple occasions, the highest severity (severe > moderate > mild) recorded for the event will be presented in the AE by severity summary. Similarly, if a subject has the same AE on multiple occasions, the closest relationship to study drug (related > not related, where related includes definitely related, probably related, and possibly related; and not related includes probably not related and definitely not related) recorded for the event will be presented in the AE by relationship summary.

Renal impact defined by baseline GFR subgroup will be summarized for TEAE and SAE by System Organ Class and Preferred Term.

Age subgroup (age < 55 and age ≥ 55 at baseline) will be summarized for TEAE and SAE by System Organ Class and Preferred Term.

All AEs will be included in the listings. Supporting listings of SAEs, AEs leading to study discontinuation, and AEs leading to death will be provided. Subjects with PDEAEs in the Follow-up Period will also be listed.

3.6.3. Deaths, Serious and Other Significant Adverse Events

The number and percentage of subjects with at least one SAE (regardless treatment emergent or not) will be summarized by System Organ Class and Preferred Term for the Safety Population. Deaths and AEs leading to discontinuation (regardless treatment emergent or not) will be summarized similarly.

Supporting listings of serious AEs and AEs leading to study discontinuations will be provided.

Subjects who died during the study will also be listed.

3.6.4. Adverse Events of Special Interest

Adverse events in the following categories of interest will be presented by system organ class and preferred terms:

- Anaphylaxis and Angioedema (serious events only)
- Infections (including progressive multifocal leukoencephalopathy (PML) and opportunistic infections) (serious events)
- Opportunistic infections
- Lymphopenia and Lymphopenia (lymphocyte relevant)
- Liver injury
- Malignancies
- Pre-malignant conditions
- Renal Injury
- Cardiac Disorder
- Gastrointestinal Tolerability AEs (serious or leading to discontinuation)
- Abuse potential

Supportive AE listing will be provided for each special interest group.

3.6.5. Clinical Laboratory Parameters

Laboratory parameters will be presented in conventional units. Only scheduled laboratory parameters will be included in the summaries. All laboratory data, including those collected at unscheduled visits, will be included in the listings. Laboratory results (baseline and change from baseline) for chemistry and hematology parameters for each visit during the entire study will be summarized. Percent change of lymphocyte count for each visit will be summarized.

For urinalysis, the number and percentage of subjects with abnormalities at any post-baseline visit will be summarized. In addition, the number and percentage of subjects with values considered potentially clinically significant (PCS) occurring at any post-baseline visit for selected parameters will be summarized.

Clinical laboratory test values, scheduled or unscheduled, will be considered PCS if they meet PCS criteria listed in Table 2. The percentages will be calculated relative to the number of

subjects with available non-PCS baseline values with respect to the specific criterion and at least 1 post-baseline assessment. The numerator is the total number of subjects with a non-PCS baseline value with respect to the specific criterion and at least 1 post-baseline PCS value. A supportive listing will present all values for a parameter for subjects with at least one PCS value for that parameter.

Shift tables for shift from baseline to any post baseline visits during treatment period will be provided for selected chemistry, hematology, and urinalysis parameters with conventional reference limits (limits provided by the performing laboratories) for the Safety Population.

The following graphical displays will be presented by enrollment group and overall:

- Mean along with the corresponding standard error (SE) for selected chemistry and hematology laboratory parameters.
- Boxplots will be used to display summary statistics for the last assessment, maximum and minimum change from baseline values for selected chemistry and hematology laboratory parameters.

Pregnancy and drug test data will be listed.

Table 2: Criteria for Potentially Clinically Significant (PCS) Laboratory Parameters

Category	Parameter	Criteria
Hematology	Hematocrit	≤ 32% and 3 point decrease from baseline (Female) ≤ 37% and 3 point decrease from baseline (Male)
	Hemoglobin	≤ 9.5 g/dL (Female) ≤ 11.5 g/dL (Male)
	Neutrophils	< 1.5×10^3/uL
	Platelets	< 75.1×10^3/uL ≥ 700×10^3/uL
	WBCs - total, differential (absolute)	≤ 2.8×10^3/uL ≥ 16×10^3/uL
	lymphocytes	< 0.5×10^9/L
	Eosinophils	>1.0×10^3 cells/uL
Chemistry	ALT	≥ 3 × ULN
	Albumin	< 2.5 g/dL
	ALK-P	≥ 3 × ULN
	AST	≥ 3 × ULN
	Bicarbonate	< 15 mmol/L > 31 mmol/L
	BUN	> 30 mg/dL

Category	Parameter	Criteria
	Calcium	< 8.2 mg/dL > 12 mg/dL
	Chloride	≤ 90 mmol/L ≥ 118 mmol/L
	Creatine Kinase	> 3 × ULN
	Creatinine	≥ 2 mg/dL
	Gamma Glutamyltransferase	≥ 3 × ULN
	Glucose	< 50 mg/dL > 200 mg/dL
	HDL Cholesterol	≤ 30 mg/dL
	Lactate Dehydrogenase	> 3 × ULN
	LDL Cholesterol	≥ 160 mg/dL
	Phosphate	< 2 mg/dL > 5 mg/dL
	Potassium	< 3 mmol/L > 5.5 mmol/L
	Prolactin	> 1 × ULN
	Sodium	< 130 mmol/L > 150 mmol/L
	Thyroid stimulating hormone (TSH)	> 5.5 µIU/mL
	Total Bilirubin	≥ 2 mg/dL
	Total Cholesterol	> 300 mg/dL
	Triglycerides	≥ 120 mg/dL (Female) ≥ 160 mg/dL (Male)
	Uric Acid	> 9 mg/dL > 8 mg/dL (Female) > 10 mg/dL (Male)
Urinalysis	Glucose	at least 2+
	Protein	at least 2+

For liver function tests, the number and percentage of subjects will be summarized by upper limit of normal (ULN) category as follows:

- ALT (alanine aminotransferase), AST (aspartate aminotransferase) and ALK-P (alkaline phosphatase) will be summarized by normal, > 3 × ULN, > 5 × ULN and > 10 × ULN.

Number of subjects who meet Hy's Law criteria (total Bilirubin > 2 × ULN and ALT or AST > 3 × ULN) will be summarized and corresponding listing will be presented.

In addition, number of Subjects with Lymphopenia by Maximum NCI-CTCAE Toxicity Grade 1-4 will be summarized. A listing with all post-discontinuation lymphocyte counts from subjects who require additional lymphocyte count monitoring visits, as per the protocol, will also be provided.

3.6.6. Vital Signs and ECG Parameters

3.6.6.1. Vital Signs

Vital signs for each visit during the entire study will be summarized by enrollment group and overall. All vital signs data will be presented in the subject data listings.

Number and percentage of subjects with vital sign values considered PCS occurring at any post-baseline visit will be summarized by enrollment group and overall. Criteria for PCS are presented in Table 3 and will be presented for each criterion. The percentages will be calculated relative to the number of subjects with non-PCS baseline values with respect to the specific criterion and at least 1 post-baseline assessment. A supportive listing will present all values for a parameter for subjects with at least one PCS value for that parameter.

In addition, the figure of mean change from baseline along with the corresponding SE will be summarized by visit and enrollment group, and overall for systolic blood pressure, diastolic blood pressure, and pulse rate.

Table 3: Criteria for Potentially Clinically Significant (PCS) Vital Signs

Parameter	Criteria
Systolic Blood Pressure	Low: ≤ 90 mm Hg and decrease ≥ 20 mm Hg High: ≥ 180 mm Hg and increase ≥ 20 mm Hg
Diastolic Blood Pressure	Low: ≤ 50 mm Hg and decrease ≥ 15 mm Hg High: ≥ 105 mm Hg and increase ≥ 15 mm Hg
Pulse Rate	Low: ≤ 50 mm bpm and decrease ≥ 15 bpm High: ≥ 120 mm bpm and increase ≥ 15 bpm

3.6.6.2. Electrocardiograms

ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, QTcB [QT interval corrected using Bazett's method], QTcF [QT interval corrected using Fridericia's method]) will be summarized for each visit during the entire study by enrollment group and overall.

Number and percentage of subjects with QTcB or QTcF parameter values considered PCS occurring at any post-baseline visit will be summarized by enrollment group and overall. Criteria for PCS are presented in Table 4 and will be presented for each criterion. A subject will be counted only once in the highest category for a given parameter based on the largest post-baseline value. The percentages will be calculated relative to the number of subjects with baseline value ≤ 450 msec and at least 1 post-baseline assessment in the safety analysis set.

A supportive listing will present all values for a parameter for subjects with at least one PCS value for that parameter.

Table 4: Criteria for Potentially Clinically Significant (PCS) QTcB and QTcF Values

Parameter	Criteria
QTcB and QTcF	> 450 to ≤ 480 msec
	> 480 to ≤ 500 msec
	> 500 msec
	Change from baseline > 60 msec
	Change from baseline > 60 msec

3.6.7. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire used to measure the presence and intensity of suicidal ideation and behavior. Suicidal behavior and suicidal ideation will be summarized by enrollment group and overall. The proportion of subjects who meet the criterion for each of these categories will be summarized as described in Table 5.

Table 5: C-SSRS Categories for Analysis

Category	C-SSRS Item response is "YES"
Suicidal behavior	Preparatory acts or behavior Aborted attempt Interrupted attempt Actual attempt Complete suicide
Suicidal ideation	Wish to be dead Non-specific active suicidal thoughts Active suicidal ideation with any methods (not plan) without intent to act Active suicidal ideation with some intent to act, without specific plan Active suicidal ideation with specific plan and intent

3.7. Pharmacokinetic Data Analysis

PK analyses will be performed using the PK analysis set. Individual plasma concentrations will be listed by actual sampling times and summarized by nominal sampling times using descriptive

statistics. Plots of individual and mean concentrations over nominal time will also be generated. PK parameters will be calculated using non-compartmental analysis. Parameters will be estimated using actual elapsed time from dosing, and summarized using descriptive statistics. A subject listing of individual PK parameters will be provided.

Non-compartmental analysis will be performed to estimate the PK parameters as data allow. Additionally, PK concentration data obtained from this study will may be combined with data from other studies to develop a population PK model, which will be reported separately.

The PK parameters to be calculated includes, but is not limited to:

- C_{max}: Maximum observed concentration
- t_{max}: Time to reach C_{max}
- AUC_{last}: Area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the last observed concentration above the lower limit of quantification.

3.8. Statistical Considerations for COVID-19

Due to the Coronavirus Disease 2019 (COVID-19) public health emergency, many data collection challenges arose in this study. However, additional efforts were made to collect more data related to COVID-19, including but not limited to protocol deviations, AEs for COVID-19, COVID-19 testing and vaccine for COVID-19, concomitant medication to treat COVID-19 AEs and vaccines to prevent COVID-19, and treatment and study discontinuation due to COVID-19 etc.

The impact of COVID-19 will be evaluated for the safety population. Data for subjects who discontinued the study due to COVID-19 will be summarized with the reason for discontinuation in the listing. An overview table, including the number of subjects with TEAEs, serious AEs (SAEs) related to COVID-19, will be provided by enrollment group and overall. All AEs related to COVID-19 will be included in the listings. COVID-19 related concomitant medication data will be summarized and included in the listings. Major protocol deviations related to COVID-19 will be provided in the listings. The protocol deviations log may be used to summarize the impact of COVID-19 in this study.

4. INTERIM ANALYSES AND DATA MONITORING COMMITTEE (DMC)

Interim analyses were planned for this study for regulatory submission. Interim SAP was specified separately.

5. CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

COVID-19 impact will be assessed and summarized for major protocol deviation, AE, concomitant medication, and subject disposition.

6. DEFINITIONS AND CONVENTIONS FOR HANDLING OF DATA

Dataset specifications will be provided in a separate document.

6.1. Analysis Visit Windows

Scheduled analysis visits are visits upon scheduled time points as specified in Table 1 Schedule of Visits and Assessments.

Scheduled analysis visits during the study period will be the same as the nominal visits collected in the eCRF unless otherwise specified by the specification document for analysis datasets. There will be one valid value of assessment kept for each scheduled analysis visit in summary/ analysis statistics.

Unscheduled visits are visits with data not collected at scheduled time points. Unscheduled visits will not be used for by-visit summary/analysis statistics unless specified otherwise. All unscheduled visits will be included as collected in eCRF in listings.

6.2. Handling Of Concentration Data Below The Lower Limit Of Quantification

For PK analysis, individual < LLOQ values will be converted using the following rules:

- < LLOQ values will be set to "0" if before t_{max} or
- < LLOQ values will be set to "missing" if after t_{max} For Tables and Listings:
- For individual concentration values, the < LLOQ values are considered equal to 0 for the calculation of descriptive statistics, but reported as '< LLOQ' in concentration listings.
- For mean concentration values, if the mean is < LLOQ, '< LLOQ' is reported in concentration tables.
- For mean concentration-related PK parameter values (eg, C_{max}, C_{last}, etc.), if the mean is < LLOQ, the mean of the value is reported in the PK tables.

For Figures:

- For individual and mean figures, < LLOQ values are presented as 0 before the last sampling time point (t_{last}) for the linear representation (no value for semi-log plot), and are not presented after t_{last},

During pharmacokinetic analysis, pre-dose values that are either missing or < LLOQ will be assigned a value of zero when calculating AUC values.

PK concentration values < LLOQ will be treated as zero for the determination of summary statistics and will be treated as missing for the calculation of the geometric means. For the presentation of summary statistics, if at least 1 subject has a concentration value < LLOQ for the time point, then the minimum value will be displayed as "< LLOQ". If more than 50% of the subjects have a concentration data value < LLOQ for the time point, then the minimum and

median values will be displayed as "< LLOQ". If all subjects have concentration data values <LLOQ for the time point, then all order statistics (minimum, median, maximum) will be displayed as "<LLOQ". If the mean is less than the lower limit of quantification, the mean values will be displayed as "<LLOQ".

All original values will be presented in the by-subject listings.

6.3. Handling of Partial Dates of Concomitant Medication

Partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. In the case of completely missing stop dates, medication will be assumed to be ongoing.

6.4. Safety Data Handling

All efforts should be made to obtain the missing information from the Investigator. For C-SSRS, vital signs, laboratory testing (chemistry, hematology, urinalysis), and 12-lead ECGs, only observed data will be used for analyses, and missing data will not be imputed, except for missing and partial start dates of AEs which are handled in this study as follows:

1. Missing day: If AE start year and month are same as first dose year and month of study drug then set the missing day to first dose day; Otherwise set the missing day to 1st of the month;
2. Missing both month and day: If AE start year is same as first dose year of study drug then set the missing month and day to first dose month and day; Otherwise set the missing month and day to 1st January;
3. Missing day, month, and year: Set the missing date to first dose date of study drug; Note: If the imputed AE start date is later than AE end date then AE start date is set to the AE end date.

7. GENERAL STATISTICAL METHODOLOGY

In general, summary statistics (n, mean, SD, median, minimum, and maximum for continuous variables, and number and percentage of subjects in each category for categorical variables) will be provided by treatment group. All summary tables will be based on observed data, and missing values will not be imputed unless otherwise indicated. Measurements collected from unscheduled visits or repeated assessments will not be included in the by-visit summary tables or figures, but will be included in the derivation of the last post-baseline value during treatment, the analyses for the potentially clinically significant (PCS) post-baseline values, and subject listings. Source data for the summary tables and statistical analyses will be presented as subject data listings.

7.1. Reporting Precision

Summary statistics will be presented to the degree of precision in Table 6, unless otherwise specified:

Table 6: Degree of Precision

Statistics	Degree of Precision
Mean, Geometric mean, Median, Quartiles, Confidence limit boundaries	One more than the raw data, up to 3 decimal places.
Standard deviation, Standard error	One more than the mean, up to 3 decimal places
Minimum, Maximum	The same as the raw data, up to 2 decimal places
p-value	Rounded to 3 decimal places and therefore presented as 0.xxx; p-values smaller than 0.001 as '< 0.001'; p-values greater than 0.999 as '> 0.999'.
Percentage	One decimal place. A percentage of 100% will be reported as 100%. Percentages of zero will be reported as 0.

Fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12–0.30).

For PK concentrations and parameters the precision for summary statistics will be defined by the measurement resolution.

For weight, height, and body mass index (BMI), one decimal place will be used for summary statistics.

8. PROGRAMMING SPECIFICATIONS

Programming specifications will be provided in a separate document.

9. MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

Mock-up tables and listings will be provided in a separate document.

10. REFERENCES

1. Biogen ALK8700-A301 Clinical Study Protocol Amendment Version 5.0 (dated 27 Sep 2019)

2. Kappos, Ludwig, et al. "Inclusion of brain volume loss in a revised measure of 'no evidence of disease activity'(NEDA-4) in relapsing–remitting multiple sclerosis." Multiple Sclerosis Journal 22.10 (2016): 1297-1305.

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4. van Reenen, Mandy, and B. Janssen. "EQ-5D-5L User guide. Basic information on how to use the EQ-5D-5L instrument. Version 2.1, April 2015." (2015).

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