Official Title: A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy, and Safety Study of MTAU9937A in Patients With Prodromal to Mild Alzheimer's Disease

NCT Number: NCT03289143

Document Date: SAP Version 3: 16-August-2020

STATISTICAL ANALYSIS PLAN

TITLE:	A PHASE II, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, EFFICACY, AND SAFETY STUDY OF MTAU9937A IN PATIENTS WITH PRODROMAL TO MILD ALZHEIMER'S DISEASE
PROTOCOL NUMBER:	GN39763
STUDY DRUG:	Semorinemab (MTAU9937A, RO7105705) and [^{18}F]GTP1 (RO6880276)
VERSION NUMBER:	3
IND NUMBERS:	129270, 125702
EUDRACT NUMBER:	2017-001800-31
SPONSOR:	Genentech, Inc.
PLAN PREPARED BY:	[redacted]
DATE FINAL:	26 November 2019 final draft
DATE(S) AMENDED	4 June 2020 (Version 2) and 16 August 2020 (Version 3)

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Version 1 (3DEC2019)

Based on Version 4 of the Protocol GN39763 (11JUN2019)

Version 2 (27MAY2020)

Updated to expand the sensitivity analyses section to address intercurrent events and the impact of the COVID-19 pandemic.

Other small edits for clarity/style.

Version 3 (16AUG2020)

Updated to clarify use of alternative modeling strategies for sensitivity analyses under situations where MMRM model assumptions for the primary analysis are violated.

TABLE OF CONTENTS

1. BACKGROUND

This Phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study will evaluate the efficacy, safety and tolerability, pharmacokinetics, and pharmacodynamics of Semorinemab (MTAU9937A) in patients with prodromal-to-mild Alzheimer's Disease (AD).

MTAU9937A is a pan-tau IgG4 monoclonal antibody that has the potential to treat tauopathies (including AD and primary tauopathies). MTAU9937A is designed to bind and intercept all extracellular tau isoforms, in order to stop or slow cell-to-cell spread and propagation of tau toxicity and pathology throughout cortical and sub-cortical networks. In addition to this Phase II clinical study (GN39763), the safety and efficacy of MTAU9937A in AD is also being evaluated in the ongoing LAURIET Phase II study in moderate AD (GN40040).

Fluorine-18 Genentech tau probe 1 ([^{18}F]GTP1 or RO6880276) has been developed as a positron emitting radioligand for in vivo imaging of tau protein aggregates. [^{18}F]GTP1 has been previously evaluated in a first-in-human study (e0040) involving 3 patients with AD, 3 patients with progressive supranuclear palsy, and 2 HVs. The study demonstrated substantial retention of the radioligand in brain regions expected to contain tau pathology in patients with AD. [^{18}F]GTP1 has also been studied in two additional Phase I studies: a test re-test study (e0048) with 5 patients with AD and 5 elderly HVs, and a radiation dosimetry study (e0049) with 6 HVs. In addition, [^{18}F]GTP1 is currently being evaluated in a Phase I longitudinal natural history study (Study GN30009; clinicaltrials.gov identifier NCT02640092).

[^{18}F]GTP1 is also being evaluated in a longitudinal PET-imaging substudy of two Phase III trials of the anti-Aβ antibody gantenerumab (Studies WN29922 and WN39658; clinicaltrials.gov identifiers NCT03444870 and NCT03443973, respectively) as well as a PET-imaging substudy of a Phase II trial of the anti-Aβ antibody crenezumab (study GN28352; clinicaltrials.gov identifier NCT01998841). It also has been evaluated in a longitudinal PET-imaging substudy of two discontinued Phase II trials of the anti-Aβ antibody crenezumab (Studies BN29552 and BN29553; clinicaltrials.gov identifiers NCT02670083 and NCT03114657, respectively).

2. STUDY DESIGN

The study consists of a screening period, a double-blind treatment period, an optional OLE period, and a safety follow-up period (see protocol for details). An extended baseline visit (up to 15 days) is included in the double-blind treatment period, following randomization and prior to the initiation of study drug. Study drug (MTAU9937A or placebo) will be administered intravenously in the double-blind treatment period, and MTAU9937A will be administered intravenously in the optional OLE period. Study drug administration will occur every 2 weeks (Q2W) for the first three doses of the double-blind treatment period and every 4 weeks (Q4W) thereafter in the double-blind treatment period. MTAU9937A will be administered Q4W in the OLE period. Study treatment is defined as study drug plus the PET radioligand used during PET imaging procedures ([^{18}F]GTP1 for tau PET imaging and the amyloid radioligand for amyloid PET imaging).

This study has enrolled 457 patients at 97 sites in North America, Europe, and the Asia-Pacific region. Patients were randomly assigned to one of three active, IV dose arms (1500 mg, 4500 mg, or 8100 mg MTAU9937A) or to an IV placebo dose arm in a 2:3:2:3 (1500 mg:4500 mg:8100 mg:placebo) ratio. All patients participating in the OLE will receive

MTAU9937A 4500 mg IV. To maintain balance in dementia status and APOE status between treatment arms, randomization will be stratified by dementia status (pAD vs. mAD) and APOE status (ApoE4+ vs. ApoE4–).

2.1 OUTCOME MEASURES

2.1.1 Primary Efficacy Endpoint

Change in CDR-SB score from baseline to Week 73 (refer to Section 4.4 for detailed derivation)

2.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are as follows:

- Change in ADAS-Cog13 score from baseline to Week 73
- Change in ADCS-ADL score from baseline to Week 73
- Change in RBANS total score from baseline to Week 73
- Change in Amsterdam iADL score from baseline to Week 73

2.1.3 Safety Endpoints

The safety endpoints are as follows:

- Nature, frequency, severity, and timing of adverse events and serious adverse events. Severity of adverse events will be determined through the use of the WHO toxicity grading scale.
- Changes from baseline in vital signs, physical findings, neurologic findings, ECG, and clinical laboratory results during and following MTAU9937A administration
- Changes from baseline in suicidal ideation and behavior during and following MTAU9937A administration as assessed by the C-SSRS
- Nature, frequency, severity, and timing of neuroimaging abnormalities

2.1.4 Exploratory Biomarker Endpoints

The key exploratory biomarker endpoints are as follows:

- Change in [^{18}F]GTP1 tau PET imaging from baseline through Week 73
- Change in levels of CSF tau species from baseline through Week 73

2.2 DETERMINATION OF SAMPLE SIZE

This study enrolled 457 patients randomized to one of three active IV dose arms or to an IV placebo dose arm in a 2:3:2:3 ratio. This sample size provides reasonable precision for estimating a clinically significant treatment effect on CDR-SB scores when MTAU9937A is compared with placebo. Assuming an observed 0.6-point difference in mean CDR-SB decline between the 4500 mg MTAU9937A arm and placebo at Week 73 (a 40% relative reduction in decline versus placebo), a standard deviation across patients of 2, and a 25% dropout rate, a 90% confidence interval on the population treatment effect point estimate for the CDR-SB is approximately 0.14−1.06.

The primary analysis detailed in Section 4.4 proposes the first hypothesis test for CDR-SB be a comparison between a single pooled 4500 mg and 8100 mg dose arm versus placebo (pre-dropout n = 228 and 137, respectively). Assuming a true 0.6-point difference in mean CDR-SB decline between the pooled MTAU9937A arm and placebo at Week 73 (a 40% relative reduction in decline versus placebo), a standard deviation across patients of 2, and a 25% dropout rate, this hypothesis test is expected to have 68% power at the alpha = 0.05 level.

2.3 ANALYSIS TIMING

The analysis will be conducted once all patients have either completed the Week 73 assessment or discontinued the study. At the time of analysis, treatment assignments will be unblinded to Sponsor personnel. At this time, all patients enrolled in the study will have either discontinued or transitioned into the open-label extension period of the study. All non-Sponsor personnel who are involved in the conduct of the study (e.g. patients, site monitors, and investigators) will remain blinded to treatment assignments until all patients complete the blinded safety follow-up period or transition into the OLE.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Patients will be randomly assigned to one of three active, IV dose arms (1500, 4500, or 8100 mg MTAU9937A) or to an IV placebo dose arm in a 2:3:2:3 (1500mg:4500 mg: 8100 mg:placebo) ratio. Randomization of patients will be managed by a central interactive voice or Web-based response system (IxRS) vendor using stratified permuted block randomization. The randomization will be stratified by dementia status (pAD vs. mAD) and APOE status (ApoE4+ vs. ApoE4–). The iDCC vendor periodically checks the IxRS to ensure that randomization is being performed correctly and that the correct kits are being assigned.

3.2 INDEPENDENT REVIEW FACILITY

Clinicians/raters (but not caregivers or patients) will use an electronic device to capture clinical outcome assessment (COA) data from all patients and/or caregivers enrolled in this study. This includes the primary and all secondary endpoints. COA data from the electronic device will be transmitted to a centralized database maintained by the electronic device vendor.

The COA scales and assessments for this study will be provided unless otherwise specified. Whenever possible, there should be consistency in the rater and caregiver who complete the scales for each patient throughout the duration of the study. Potential raters should be designated at each site and will receive training and be approved by the rating-scale vendor prior to being allowed to administer any cognitive assessments/ rating scales in the study. Administration of cognitive assessments/rating scales (i.e., the COAs) will be done in accordance with instructions provided in the GN39763 COA Manual and the training/documentation provided by the rating-scale vendor.

In addition, given that the primary outcome measure in this study involves subjective judgment, the adequacy of patient interviews and ratings will be monitored by an endpoint reliability program administered by the rating-scale vendor; this is considered to be an essential part of good research methodology. Prior studies have clearly demonstrated that the failure to

adequately monitor such ratings can substantially increase the risks of failed trials (Becker and Greig 2008; Kobak 2010).

Please see the GN39763 COA Manual for instructions on COA administration order, specification of list versions to use at each visit, rater roles, restrictions on raters, and additional details on COA administration and the endpoint reliability program.

3.3 DATA MONITORING

The incidence and nature of adverse events, serious adverse events, and adverse events of special interest; responses on the C-SSRS; and abnormalities in vital signs, standard safety blood tests, ECG, and MRI will be assessed on a regular basis, approximately every 3-4 months, by an unblinded iDMC. The unblinded iDMC may also receive select summary statistics of COA endpoints.

At each safety review meeting, the iDMC will meet in a closed session to recommend whether the study should continue without modification, continue with minor modification, continue with substantial modification, suspend enrollment or treatment, or be terminated. There are currently no planned interim analyses to stop the trial early for either futility or clear signs of efficacy. Details of the iDMC are provided in the iDMC Charter.

The Sponsor also monitors all safety data continuously on a blinded basis.

4. STATISTICAL METHODS

The primary statistical analyses will be performed using SAS software (Version 9.2 or higher). R software (Version 3.3.2 or higher) may be used for creating figures, for QC purposes, and for sensitivity and subgroup analyses.

4.1 ANALYSIS POPULATIONS

Two analysis populations are defined for this study: the modified intend-to-treat (mITT) population and the safety-evaluable population.

4.1.1 Modified Intent-to-Treat Population

Efficacy analyses for each endpoint will be performed on the modified intent-to-treat population (mITT). For the primary and each secondary endpoint, the mITT population will include all randomized patients that have both a baseline measurement and at least one post-baseline measurement for the primary endpoint. The treatment groups will be based on the treatment assigned at randomization.

4.1.2 Safety-Evaluable Population

The safety-evaluable population will include all patients who were randomly allocated and received at least one dose of study drug (MTAU9937A or placebo) during the double-blind treatment period with treatment groups defined according to actual treatment received.

4.2 ANALYSIS OF STUDY CONDUCT

The number of patients who enroll, discontinue (early discontinuation of treatment or early termination from the study), complete the study (through Week 73), and continue into the OLE will be tabulated by treatment group. Reasons for early discontinuation of treatment or early termination from the study will be listed and summarized by treatment group. Any eligibility criteria exceptions and other major protocol deviations will also be summarized by treatment group.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics such as age, sex, race, ApoE4 status, and baseline MMSE score will be summarized with means, standard deviations, medians, and ranges for continuous variables and with frequencies and proportions for categorical variables, as appropriate. Summaries will be presented by treatment arm and overall.

4.4 EFFICACY ANALYSIS

All efficacy analyses will be based on the modified intent-to-treat populations defined in Section 4.1.2. The primary and secondary endpoints will be analyzed as change scores, calculated as follows:

Outcome measure change score = (post-baseline value – baseline value)

In the above determination of change score for CDR-SB and RBANS, the baseline value will be defined as the average of all non-missing values before the first dose of study drug, which should be an average of the screening and baseline values. For all other cognitive and biomarker endpoints, baseline value will be defined as latest observed value before the first dose of study drug.

For the primary and secondary endpoints, mean changes from baseline will be compared across treatment arms using mixed-models for repeated measures (MMRM).
Each model will have an intercept term, a term for baseline value of the endpoint, a term for APOE4 strata (carrier vs. non-carrier), a term for dementia status strata (pAD vs. mAD), an interaction term of the two stratification factors, categorical visit terms, a term for treatment group, a term for baseline age, and terms for treatment-by-visit interactions. This will be implemented using SAS proc mixed syntax similar to the excerpt below:

```
proc mixed data=data;
class PATNUM VISIT TRT APOE4 DEMSTATUS;
model var = BASE BAGE APOE4 DEMSTATUS APOE4*DEMSTATUS VISIT TRT TRT*VISIT
/solution noint ddfm=kr;
repeated VISIT / subject=PATNUM type=UN;
lsmeans VISIT*TRT / pdiff cl alpha=0.05;
estimate 'MTAU9937A vs Placebo Wk 73' TRT -1 1/cl;
```

An unstructured variance-covariance matrix for within-subject errors will be assumed. If the unstructured covariance structure matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive

covariance structure will be used. In these cases, the sandwich estimator will be used to get the variance of the treatment effect estimator.

If model assumptions are violated (e.g. large deviations from normality of residuals), alternative modeling strategies including data transformations, permutation-based approaches, and/or robust mixed effects modeling methodology (Koller, Journal of Statistical Software 2016) will be used as appropriate for additional sensitivity analyses.

Comparisons of Interest

Comparisons of efficacy will be performed between each MTAU9937A treatment arm and the placebo group by first pooling data from the middle and high doses for the first statistical test of the primary endpoint and then subsequently testing each treatment arm individually. Thus, there will be four comparisons across the doses:

MTAU9937A dose groups for hierarchical testing:

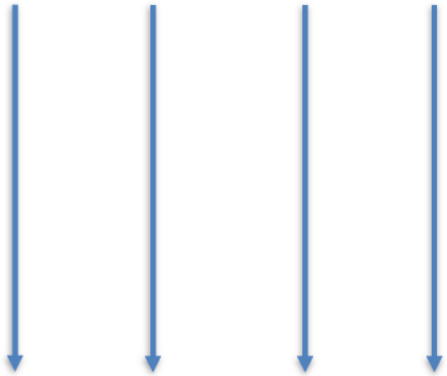
- **Group 1**: MTAU9937A 4500 mg + MTAU9937A 8100 mg vs placebo
- **Group 2**: MTAU9937A 4500 mg vs placebo
- **Group 3**: MTAU9937A 8100 mg vs placebo
- **Group 4**: MTAU9937A 1500 mg vs placebo

One model pooling middle and high doses will be used to test the Group 1 hypothesis. A second model including all 3 active arms separately will be used for Groups 2-4.

Type I Error Management

Type I error for the primary endpoint will be controlled using a fixed sequence testing procedure at the two-sided 5% significance level. The testing procedure will proceed with comparisons following the order across the four dose groups detailed above. After the first hypothesis test, each subsequent hypothesis will only be formally tested if the preceding one is significant at the 5% level.

For each dose group that has a significant result for the hypothesis test for the primary endpoint, a separate fixed sequence testing procedure will be ungated for that dose group's secondary endpoints that will similarly proceed at the 5% level. The overall testing procedure is detailed visually in the table below.

	Endpoint	MTAU9937A Dose group Group 1| Group 2 | Group 3 | Group 4
Primary	Change in CDR-SB score from baseline to Week 73	
Secondary	1. Change in ADAS-Cog13 score from baseline to Week 73 2. Change in ADCS-ADL score from baseline to Week 73 3. Change in RBANS total score from baseline to Week 73 4. Change in Amsterdam iADL score from baseline to Week 73	

No control for type I error will be applied for the exploratory endpoints, including sensitivity, subgroup, and biomarker analyses. Efficacy analyses will not involve formal comparisons between the MTAU9937A treatment arms.

4.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of MTAU9937A compared with placebo on the basis of CDR-SB change from baseline at Week 73 (with baseline defined as the average of available measurements before first dose which is expected to include both screening and baseline values).

The estimand of interest (the mITT estimand) is the mean absolute difference in CDR-SB change from baseline at Week 73 between active drug and placebo. It will be estimated using all randomized patients who received at least one dose of study drug, regardless of adherence to the assigned study treatment or to the protocol.

The MMRM approach described in Section 4.4 should provide a reasonable estimate of the mITT estimand. Mean change from baseline will be estimated at each post-baseline timepoint for each study arm (placebo and each treatment arm) using least squares means and 95% confidence intervals. The absolute difference in mean change from baseline will be estimated for each treatment arm compared with placebo using least-squares mean estimates from the MMRM model along with 95% confidence intervals.

4.4.2 Secondary Efficacy Endpoints

Secondary endpoints listed below will similarly be analyzed and reported using the methods described in Section 4.4.1 using the MMRM model described in Section 4.4. The secondary endpoints for this study are listed below:

- Change in ADAS-Cog13 score from baseline to Week 73
- Change in ADCS-ADL score from baseline to Week 73
- Change in RBANS total score from baseline to Week 73
- Change in Amsterdam iADL score from baseline to Week 73

4.4.3 Sensitivity Analyses

Mixed-models for repeated measures (MMRM) methods have been selected for the primary and secondary analyses due to their ability to accommodate the potential effects of missing data. An advantage of such models is that they rely on the assumption that the missing data mechanism is missing-at-random (MAR), rather than the more restrictive assumption that it is missing-completely-at-random (MCAR).

To evaluate the robustness of MMRM analyses to potential effects of missing data and validity of the MAR assumption, sensitivity analyses will be performed in the mITT population for the co-primary and secondary endpoints. At each time point (Week 25, Week 49, and Week 73), an ordinary least squares model for the change scores at that timepoint will be fit to estimate the treatment effect. These models will have terms for the baseline value of the endpoint, APOE4 strata, dementia status strata, the interaction between APOE4 strata and dementia status strata, baseline age, and treatment effect. These models will be fit using the following imputations for missing data:

- No imputation (a completer analysis)
- Using linear extrapolation imputation based on the values at baseline and the last week with a non-missing value
- Using last-observation-carried-forward
- Tipping point analysis

Intercurrent events may also influence the primary endpoint even if they do not directly result in missing data. Additional sensitivity analyses will be conducted using the above methods, but treating data collected after a given intercurrent event as missing. Proposed intercurrent events include missed study drug administration and initiation or modification of AD symptomatic concomitant medications. A separate section detailing intercurrent events and protocol deviations due to COVID-19 is included below. We propose to apply the same set of sensitivity analyses listed above when considering this additional set of intercurrent events.

Additional analyses looking at treatment effect estimates in subpopulations of patients receiving at least a minimum number of doses will also be conducted to assess if any observed treatment effect could have been potentially diluted by patients who did not fully adhere to the study drug administration schedule.

COVID-19 Sensitivity Analyses

Trial conduct in the double-blind period of most TAURIEL subjects up until their respective Week 49 visits was unimpacted by COVID-19, with roughly 1/3 of subjects completing the entire double-blind period with zero impact. For subjects that were still active in the double-blind period during the COVID pandemic, the following additional measures were taken to mitigate the effect of COVID-19 on drug exposure and data collection:

- Some subjects received blinded study drug administration remotely at their homes. Adverse events were also collected at these visits.
- A subset of COAs, including CDR-SB and ADCS-ADL (primary and secondary endpoints), were administered over the phone if subjects were unable to travel to clinic.

At-home study drug administration has been flagged so as to allow for a comparative safety assessment between in-clinic and at-home dosing. Similarly, phone COAs have been flagged to enable sensitivity analyses including/excluding phone COAs as their quality may be seen as less reliable. Although phone COAs have been explicityly allowed since version one of the protocol, all phone COA assessments were only collected as a result of the COVID-19 pandemic.

Protocol deviations due specifically to the COVID-19 pandemic have been flagged. Each subject's first COVID-19 protocol deviation will be treated as an intercurrent event indicating the earliest timepoint at which a given subject's trial conduct was meaningfully affected by the pandemic. All data points after this first protocol deviation are then flagged as "post-COVID" on a per-subject level and treated as missing for sensitivity analyses. Similarly, sensitivity analyses using a single date applied broadly to all subjects using a sliding window will be used as an alternative means to exclude "post-COVID" data. As mentioned previously, missed study drug administration is treated as a post-randomization event and can be identified as COVID-related or not from the protocol deviation log.

4.4.4 Subgroup Analyses

Exploratory subgroup analyses of the primary efficacy endpoint will be performed to evaluate the consistency of the primary analysis results across pre-specified subgroups defined by demographic and baseline characteristics. The following subgroups will be analyzed with respect to the primary efficacy endpoint:

- Age ($\leq$ 65 years, > 65 years)
- Sex (male, female)
- Dementia status (prodromal, mild)
- APOE4 status (positive, negative)
- Geographic region (North America, EU, rest-of-world)

Biomarker subgroup analyses are specified in Section 4.4.5.

For above subgroup analyses, a MMRM model as specified for the primary analysis in Section 4.4 will be used for each subgroup analyses based on the available data subset for the patient subgroup of interest with the exception of the dementia status and APOE4 status subgroup analyses (bullets 3 and 4) which will not contain the respective indicator variables since they are being used to define the subgroup.

4.4.5 Biomarker Analyses

Biomarker subgroup analyses

Additional biomarker analyses will be performed to further evaluate the treatment benefit in biomarker-defined patient subpopulations based on baseline levels of tau pathology as measured by [^{18}F]GTP1 which was collected from roughly 85% of patients at baseline.

Based on the primary and secondary efficacy endpoints, the treatment benefit will be assessed for the following pre-specified biomarker-defined patient subpopulations:

- **[^{18}F]GTP1 at baseline:** [^{18}F]GTP1-high patients will be defined as having a temporal meta-ROI SUVR ≥ 1.3. [^{18}F]GTP1-low patients will be defined as temporal meta-ROI

SUVR < 1.3 (Jack et al., Brain 2017). From the baseline data, roughly 75% of patients who received a [^{18}F]GTP1 scan were defined as [^{18}F]GTP1-high at the baseline visit.

Additional sensitivity analyses will be conducted to assess the robustness of the proposed SUVR threshold and region of interest for defining [^{18}F]GTP1-high vs low.

An MMRM model similar to that specified for the primary and secondary analyses will be used for each subgroup analysis based on the data subset for the biomarker subgroup of interest. Point estimates for the treatment benefit within each biomarker patient group as defined above will be presented along with 95% confidence intervals and p-values.

Pharmacodynamic biomarker analyses

[^{18}F]GTP1 has been identified as a key exploratory imaging PD biomarker. [^{18}F]GTP1 whole cortical gray SUVR change from baseline will similarly be analyzed and reported using the MMRM model described in Section 4.4. In addition to whole cortical gray SUVR, other exploratory [^{18}F]GTP1 ROIs and metrics of tau spread will be explored.

Several candidate fluid PD biomarkers have been identified (e.g. multiple CSF assays for different tau species and plasma tau measures) and will be measured to assess the effect of MTAU9937A. Descriptive summaries of the PD biomarker values at each visit, as well as changes from baseline will be summarized by treatment arm.

4.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of either MTAU9937A or placebo, or GTP1, with patients grouped according to treatment arm. Patients will be analyzed according to actual MTAU9937A treatment received.

All adverse events that occur after informed consent is given will be summarized by MedDRA mapped term, appropriate thesaurus level, and toxicity grade. In addition, all serious adverse events, including deaths and events leading to discontinuation, will be listed separately and summarized.

Laboratory data will be summarized by descriptive statistics by treatment group.
In addition, all laboratory abnormalities will be summarized by grade using the WHO grading scale.

Dose-limiting adverse events and adverse events of special interest will be listed and summarized by treatment group.

Vital signs (pulse rate, blood pressure, body temperature, and respiratory rate), weight, and other disease-specific data will be summarized by descriptive statistics by treatment group. Changes from baseline will be summarized by treatment group.

4.6 MISSING DATA

A careful examination of reasons for study discontinuation will be conducted to assess the nature of incomplete data. In addition, frequencies and percentages of missing data at Week 73 will be compared between the two treatment arms. Missing data will not be imputed for the

primary analysis, but will instead be handled via the missing-at-random (MAR) assumption from the MMRM model as described in Section 4.4. Analyses to explore the sensitivity of results to missing data assumptions will be conducted as described in section 4.4.3. The issue of missing data for secondary and exploratory endpoints will be handled similarly with a MMRM model.

Patients who discontinue the study will be included in the analysis up to the date of study discontinuation.

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