NOVARTIS

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

BLZ945

CBLZ945C12201 / NCT04066244

An open-label, adaptive design study in patients with amyotrophic lateral sclerosis (ALS) to characterize safety, tolerability and brain microglia response, as measured by TSPO binding, following multiple doses of BLZ945 using positron emission tomography (PET) with the radioligand [^{11}C]-PBR28

Statistical Analysis Plan (SAP)

Author(s): Personal Protected Data (PPD)

Document type: SAP Documentation – NIBR

Document status: Amendment 3

Release date: 7-Mar-2024

Number of pages: 24

Commercially Confidential Information (CCI)

Table of contents

Commercially Confidential Information

List of tables

List of figures

1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CBLZ945C12201".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

Study protocol (v06) is available at the time of finalization of Statistical Analysis Plan.

1.3 Study objectives

1.3.1 Primary Objective(s)

Primary objective(s)	Endpoints related to primary objective(s)

• Cohorts 1-4 and Cohort 5 (PET Sub-study): To evaluate brain microglial reduction, as measured by reduction in TSPO binding, following treatment with BLZ945 in ALS participants by using PET imaging with [^{11}C]-PBR28	• Volume of distribution (Vt) in different brain regions for each [^{11}C]-PBR28 PET scan, and change after BLZ945 treatment
	  • Cohorts 1-4: at Day 5 (or 8) following 4 (or 7) oral doses of BLZ945 compared to baseline
	  • Cohort 5 (PET sub-study): at Week 12 following repeated cycles of BLZ945 compared to baseline

• Cohort 5: To assess safety-related effects on ECM accumulation under BLZ945 treatment	• Cohort 5: Changes in esophageal wall thickness (based on CT-scans) at Week 12 compared to baseline • Cohort 5: Cardiac valve thickness, cardiac valve function (stenosis and regurgitation based on echocardiography) and Left Ventricular Ejection Fraction (LVEF) as indicator of cardiac function (based on echocardiography) at Week 12 compared to baseline • Incidence of AEs related to ECM accumulation during the first 12 weeks of treatment

1.3.2 Secondary Objective(s)

Secondary objective(s)	Endpoints related to secondary objective(s)

• Cohorts 1-5: To characterize the pharmacokinetics (PK) of BLZ945 in participants with ALS.	• Cohort 1-4: • Plasma: PK parameters on Day 1 and Day of last treatment (Day 4 or Day 7) (e.g. Cmax, Tmax, AUC, T1/2). Urine: renal clearance (CLR) on Day 1 and Day of last treatment (Day 4 or Day 7) • Cohort 5: BLZ945 plasma concentrations and selected PK parameters (Cmax, Tmax, AUClast, Tlast) on Day 1 (Arm #2) and Day 4 (Arm #1) as feasible
• Cohorts 1-5: To evaluate safety and tolerability of BLZ945 in participants with ALS at the planned doses and dosing regimen.	• Cohorts 1-5: Relevant clinical findings - as per assessment schedule - on physical examination, neurological examination, vital signs, hematology, chemistry, urinalysis, ECG evaluation, AE and SAE recordings during the entire duration of the study (including extended treatment period)
• Cohorts 1-5: To assess the CYP2C8 pharmacogenomic-pharmacokinetic relationship	• CYP2C8 genotypes and BLZ945 plasma PK parameters

Commercially Confidential Information

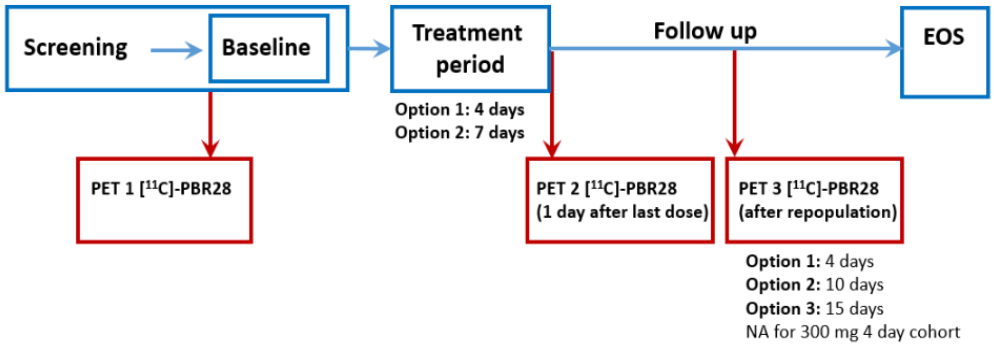
1.4 Study design and treatment

1.4.1 Cohorts 1-4:

This study is an exploratory, adaptive, open-label study of a single treatment cycle of multiple oral doses of BLZ945 in ALS participants, administered using either a 4 days on / 10 days off or a 7 days on 7 days off treatment regimen.

The first four cohorts in the study consist of an up to 42-day screening and baseline period, a treatment period of a minimum of 4 days and a maximum of 7 days, a follow-up period until day 36 (for 4 day cohorts) or day 40 (for 7 day cohorts) (during this period repopulation of microglia will be assessed); see Figure 1-1. The maximum study duration for each participant, including the 42-day screening visit, is 80 days for the 4-day cohorts and 84 days for the 7-day cohort.

Figure 1-1: Study Design Cohorts 1-4



This is a multiple ascending dose study with the starting dose of 300 mg daily for four days. After each dosing cohort and before proceeding to the next cohort, a review of all available data will be conducted, including pharmacodynamic (PD) (% microglial reduction), and safety/tolerability (continued review of adverse events, laboratory assessments, blood pressure and ECG data) data. PK data from the first three dosing cohorts (planned as 300 mg, 600 mg, 1200 mg) will be reviewed after the third dosing cohort prior to proceeding to the fourth dosing cohort. The PK review will be done to assist with the determination of the appropriate next dose(s). The PK data may be reviewed prior to the initiation of any dosing cohort should this information be determined by the Investigators and/or Sponsor as necessary for decision-making purposes. The decision to proceed to the next dose cohort will be made jointly between the Sponsor and the Investigator.

1.4.2 Cohort 5:

Cohort 5 will consist of an open-label, randomized, two-arms study investigating two BLZ945 dosing regimens. Participants with confirmed diagnosis of ALS will receive repeated treatment cycles of BLZ945 either 4 days on followed by 10 days off or once weekly. Cohort 5 CCI

PET sub-study will recruit approximately 8 participants. Enrollment may continue up to a maximum of 40 participants overall.

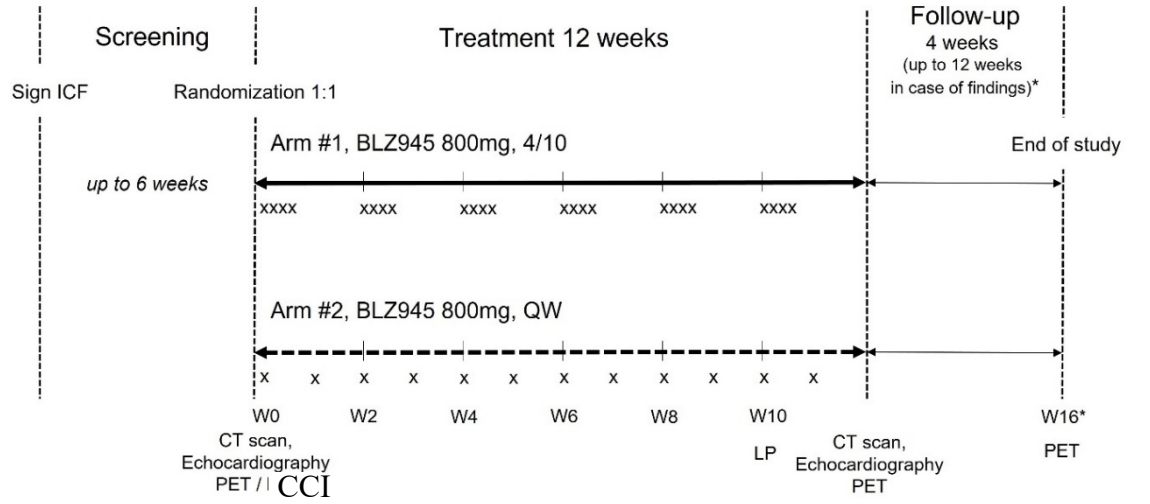
The cohort includes a screening period (up to 6 weeks), a 12-week open-label treatment period, followed by a 4-week safety follow-up (Figure 1-2). Participants who consent and are eligible may continue to an additional 24-week extended treatment period on the same regimen (Figure 1-3).

Participants will be randomized in a 1:1 ratio across two dosing regimens: Arm #1: 800 mg BLZ945 in repeated cycles of 4 days on treatment followed by 10 days off treatment (4/10) or Arm #2: 800 mg BLZ945 once a week (QW).

Participants previously screened or dosed in Cohorts 1 to 4 may be enrolled in Cohort 5 if they meet eligibility criteria.

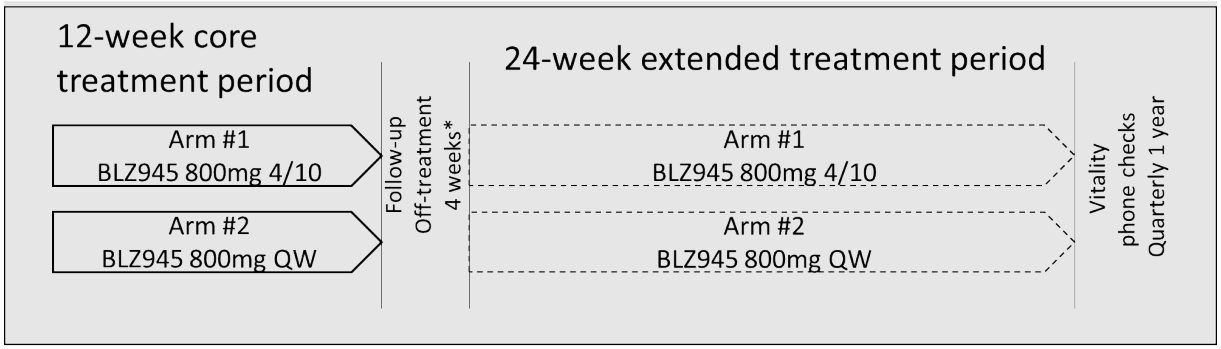
A PET sub-study will enroll approximately 8 participants at specific study sites. CCI

Figure 1-2 Study design Cohort 5



x = drug administration
W = week of treatment
* 4 weeks follow up in all participants + 8 weeks for recovery in participants with findings
# Cohort 5 Commercially Confidential Information

Figure 1-3 Study design Cohort 5 including the 24-week extended treatment period



* 4 weeks follow up in all participants + 8 weeks for recovery in participants with findings

2 First interpretable results (FIR)

Commercially Confidential Information

3 Interim analyses

Commercially Confidential Information

4 Statistical methods: Analysis sets

For all analysis sets, which is identical to the safety analysis set, participants will be analyzed according to the study treatment(s) received.

The full analysis will include all participants who received any study drug.

The PK analysis set (PAS) will include all participants with at least one evaluable (i.e., not flagged for exclusion) PK concentration measurement.. For a BLZ945 plasma concentration to be considered evaluable, a subject must:

- Have received a protocol planned dose.
- For pre-dose samples, do not vomit within 4 hours after the dosing of BLZ945 prior to sampling.
- For post-dose samples, do not vomit within 4 hours after the dosing of BLZ945.
- For pre-dose sample, have the sample collected before the next dose administration and 18-30 hours after the last dose administration.
- Administer BLZ945 under fasted state (at least one hour before or two hours after meal).
- No protocol deviations that impact PK data.

Additionally for arm 1 day 4 BLZ945 plasma sample, the above conditions must also be met for all four doses from day 1 to day 4.

Commercially Confidential Information

Commercially Confidential Information

Any blood samples with missing collection date or time, or missing associated study drug dosing date or time will be excluded. Additionally, a PK sample can be considered not evaluable as per scientific judgment of the clinical pharmacology expert. In such case, the PK sample is excluded from the analyses and the reason for its exclusion will be documented.

The PD analysis set will include all participants with available PD data and no protocol deviations with relevant impact on PD data.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Participants are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
INCL##	*Xxxxxxx*	
EXCL##	*Xxxxxxx*	
Participants are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
INCL##	*Xxxxxxx*	
EXCL##	*Xxxxxxx*	
Participants are excluded from PK and PD analysis in case of these PDs:		Exclude subject from PK and PD analysis sets
INCL##	*Xxxxxxx*	
EXCL##	*Xxxxxxx*	

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

All participants within the PK analysis set will be included in the PK data analysis.

5.1 Variables

Cohort 1-4: Plasma PK parameters on Day 1 and Day of last treatment (Day 4 or Day 7) (e.g. Cmax, Tmax, AUC_{last}, AUC_{0-24}, T1/2, Racc). Urine: renal clearance (CLR) on Day 1 and Day of last treatment (Day 4 or Day 7)

Cohort 5: BLZ945 plasma concentrations and selected PK parameters (Cmax, Tmax, AUClast, Tlast) on Day 1 (Arm #2) and Day 4 (Arm #1) as feasible.

Other plasma or urine PK parameters will be determined as appropriate.

5.2 Descriptive Analyses

Cohorts 1-4

Commercially Confidential Information

Summary statistics of BLZ945 pharmacokinetic parameters will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented. A geometric mean will not be reported if the dataset includes zero values. Descriptive graphical plots of individual plasma concentration versus time profiles and mean concentration versus time profiles will be generated. Further graphical exploratory analysis will be carried out if deemed appropriate.

Cohort 5

Commercially Confidential Information

Summary statistics of BLZ945, Commercially Confidential Information pharmacokinetic parameters will include mean (arithmetic and geometric), SD, CV (arithmetic

and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented. A geometric mean will not be reported if the dataset includes zero values. With only 4 samples and only up to 4 hrs post dose, it may not be possible to derive the PK parameters above.

Cohorts 1-5

The relationship between CYP2C8 polymorphisms and BLZ945 PK parameters will be assessed graphically and descriptively.

6 Statistical methods for Pharmacodynamic (PD) parameters

All participants within the PD analysis set will be included in the PD data analysis.

All primary, secondary CCI PD endpoints listed below will be analyzed using the same statistical methodology for all cohorts unless explicitly detailed for Cohort 5.

For Cohort 5 secondary and exploratory PD endpoints assessing the change from baseline to Week 40, the change from baseline to be summarized primarily refers to the change from the baseline prior to BLZ945 drug administration of the core period. Additional summaries for the change from start of the extended treatment (Week 16) will also be included as applicable.

6.1 Primary objective(s)

Cohorts 1-4 and Cohort 5 (PET Sub-study): To evaluate brain microglial reduction, as measured by reduction in TSPO binding, following treatment with BLZ945 in ALS participants by using PET imaging with [^{11}C]-PBR28

Cohort 5: To assess safety-related effects on ECM accumulation under BLZ945 treatment

6.1.1 Variables

Cohorts 1-4

The percent change in Vt of the first scan 24 hours after last BLZ945 treatment relative to baseline will be considered as primary endpoint.

Cohort 5

The percent change from baseline to Week 12 in Vt measured via PET scan.

The changes from baseline to Week 12 in: esophageal wall thickness (mm), and LVEF (%)

Any worsening from baseline to Week 12 in cardiac valve thickness and cardiac valve function (stenosis and regurgitation).

Adverse events of ECM accumulation during the 12 weeks of treatment.

6.1.2 Descriptive analyses

Cohorts 1-4

The microglia depletion (raw and % percent change from baseline) will be listed by dose cohort, subject and visit time. Descriptive summary statistics for raw and % percent change from baseline will be provided by dose cohort and visit/time.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. A geometric mean will not be reported if the dataset includes zero values.

Cohort 5

Descriptive statistics will be provided by treatment and visit for the Cohort 5 for efficacy and safety endpoints. No formal statistical comparison will be carried out between the two treatment arms. For continuous measures, such as percent change from baseline to week 12 in Vt measured via PET scan, esophageal wall thickness change from baseline to week 12 and LVEF change from baseline to week 12, the mean, SD and 95% CI will be provided by treatment arm. For measures such as cardiac valve function (stenosis and regurgitation based on echocardiography) and cardiac valve thickness, the number and frequency of participants with any worsening between baseline and Week 12 will be presented by treatment arm, as well as the 95% CI for the rate based on the Wilson method. Number and percentages of participants with AEs of ECM accumulation will be summarized by treatment arm.

6.1.3 Statistical model, assumptions and hypotheses for Cohorts 1-4

The fraction of brain microglia reduction following four oral doses of BLZ945 will be analyzed by an Emax model with dose as the independent variable and reduction fraction as the dependent variable. Allometric scaling of a mouse PK/PD model makes it credible that 4 doses at 600 mg for 4 days will lead to a 50% reduction in microglia 18 days past the 4th dose. The same model points to a Hill constant between 1 and 3.3. It hence seems reasonable to analyze all available microglia reduction data at the 5 day time point by a sigmoidal Hill constant model with prior distributions on the EC50 of 600 mg and Hill constant centered at 2. Such a model assumes that the microglia reduction after 4 doses is independently normally distributed among participants with a mean which can be expressed by a two-parameter Emax function. If the microglia depletion fraction at concentration c is denoted Y(c), then the model assumes that

$$Y(c) = c^h / (c^h + D^h) + \text{error}$$

Here, D and h are the two unknown parameters, the concentration giving a 50% response and the Hill constant.

For the purposes of this study, brain [^{11}C]-PBR28 binding reduction of 20% or more has been chosen as sufficient evidence of target engagement to enable further development.

6.1.3.1 Model checking procedures for Cohorts 1-4

No imputation of missing values will be considered for the primary analysis.

6.1.3.2 Graphical presentation of results for Cohorts 1-4

The relationship between the microglia depletion ratio and BLZ945 dose level obtained from the model described in section 6.1.3 will be presented graphically.

6.1.4 Sensitivity and Supportive analysis for Cohorts 1-4

It will be assessed through residual plots whether the model of the primary analysis gives a credible description of data. Other models with transformed response, non-constant error variance, and baseline covariates included may be attempted in order to see if the dose-response fit and conclusions hold up.

If substantial dropouts are seen prior to study day 4 (so that the primary end point is missing), the dose-response relationship will be reassessed under a model for informative drop out. This will be done in order to ensure that potential non-responders are not more likely to drop out.

The log-ratio-to-baseline of Vt will be analyzed using a one sample t-test for each PET scan, specifically for PET2 and PET3 and by brain region. The results will be back- transformed where the estimated geometric mean ratio, 90% confidence interval of the mean ratio and corresponding 2-sided p-value will be reported.

6.2 Secondary objectives

A secondary objective of this study is to evaluate the safety and the brain microglia reduction following multiple oral doses of BLZ945 in ALS participants.

6.2.1 Descriptive analyses

The safety and tolerability will be evaluated by the following standard safety assessments; relevant findings from physical and neurological examinations, vital signs, hematology, chemistry, urinalysis, ECG evaluation, AE and SAE recordings. For Cohort 5, AEs potentially related to ECM accumulation or vasculitis will be summarized. The evaluations will be mostly descriptive; should a dose-dependent incidence in AEs be present, it will be quantified by Cochran-Armitage test for trend.

Commercially Confidential Information

7 Statistical methods for safety and tolerability data

All participants within the Full Analysis Set (FAS) will be included in the safety data analysis.

All primary, secondary and exploratory safety endpoints listed below will be analyzed using the same statistical methodology for all cohorts unless explicitly detailed for Cohort 5.

For Cohort 5 secondary and exploratory safety endpoints assessing the change from baseline to Week 40, the change from baseline to be summarized primarily refers to the change from the baseline prior to BLZ945 drug administration of the core period. Additional summaries for the change from start of the extended treatment (Week 16) will also be included as applicable.

7.1 Variables

Safety and tolerability assessments including adverse events, cardiovascular safety parameters (ECG, vital signs), Columbia Suicide Severity Rating Scale questionnaire (C-SSRS), and general safety parameters (blood and urine laboratory parameters, physical examination) will be collected.

7.2 Descriptive analyses

Participant demographics and other baseline characteristics

For Cohorts 1-4, demographic and other baseline data will be summarized descriptively by dose cohort. For Cohort 5, demographic and other baseline data will be summarized by treatment arm.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. Differences from baseline of continuous variables will be presented in the same way.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, and by dose cohort.

Treatment

The duration of exposure to BLZ945 will be summarized by means of descriptive statistics using the safety set. For Cohorts 1-4, numbers of participants exposed to the different daily doses of BLZ945 will be tabulated. For Cohort 5, numbers of participants exposed to the different treatment arms will be tabulated.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by dose cohort.

Vital signs

All vital signs i.e. body temperature, blood pressure and pulse measurement data will be listed by dose cohort, subject, and visit/time and if ranges are available abnormalities will be flagged. Summary statistics will be provided by dose cohort and visit/time.

ECG evaluation

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

C-SSRS

Summary statistics showing the number of Patients with Suicidal Ideation, Suicidal Behavior, and Self Injurious Behavior without Suicidal Intent Based on the C-SSRS during treatment, will be produced by dose cohort. The C-SSRS during treatment data will be listed by dose cohort, subject, and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by dose cohort, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by dose cohort and visit/time.

The liver lab parameters (ALT, AST, ALK, BILI) may also be summarized spaghetti plots where the observations are converted into multiples of ULN (e.g. observed value/ULN for the given lab parameter) and are plotted over time for each subject.

To identify potential Hy's Law cases, the eDISH (evaluation of Drug-Induced Serious Hepatotoxicity) plot may be used. A log/log display of correlation between peak TBIL vs. peak ALT, both in multiples of ULN, with horizontal and vertical lines indcating Hy's law thresholds e.g. ALT = 3 x ULN and TBIL = 2 x ULN. The eDISH plot makes immediately evident subjects potentially matching Hy's law laboratory criteria, all located in the upper right quadrant of the graph. Observations may also be color coded by treatment or by subject.

Adverse events

All information obtained on adverse events will be displayed by dose cohort and subject.
The number (and percentage) of patients with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, AEs of special interest potentially related to risks resulting from BLZ945 treatment (e.g. ECM accumulation, vasculitis) and adverse events leading to dose adjustment.

A patient with multiple adverse events within a body system is only counted once towards the total of this body system and treatment.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Should a dose dependent incidence in AEs be present, it will be qualified by Cochran-Armitage test for trend.

Adverse events of special interest / grouping of adverse events in Cohort 5:

Gastrointestinal toxicity and skin toxicities are identified risks for BLZ945. Hepatic effects, muscle effects, accumulation of extracellular matrix, QT prolongation, vasculitis, pancreatitis, effects on lymphoid organs, drug-drug interactions, effects on endocrine organs and effects on bones are potential risks related to BLZ945. In addition, suicidal ideation and behaviour and reproductive and developmental toxicity are also adverse of interest for BLZ945. The search criterion for each of these risks and events of interest will be defined based on MedDRA and on the BLZ945 Case Retrieval Strategy (eCRS).

The most recent eCRS at the time of database lock will be used to determine the MedDRA search criteria to identify events of special interest.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

8 Pharmacokinetic / pharmacodynamic relationships

All participants within the PK/PD analysis set will be included in the PK/PD data analysis.

To evaluate the relationship between systemic PK (i.e. Cmax, AUC0-24 and AUClast) and PD markers such as AST/ALT, and peripheral monocyte counts.

8.1 Variables

Cohorts 1-4: BLZ945 PK parameters on Day 1 and Day of last treatment (Day 4 or Day 7) versus other PD markers.

Cohort 5: Estimated individual BLZ945 PK levels or parameters on Day 4 (Arm #1) or on Day 1 (Arm #2) and/or on Week 10 vs other PD markers.

8.2 Descriptive analyses

Cohorts 1-4: The relationship between (cumulative) daily doses (and/or systemic exposure) with the brain microglia reduction, based on the volume of distribution, on the standardized uptake values ratios (SUVR), and on the percent change after repeated BLZ945 oral

administration will be investigated. All generated data at all dose levels will be pooled to explore a dose exposure response relationship.

Cohort 5: The exposure-response relationship for PET CCI will be explored.

9 Pharmacogenomic / pharmacokinetic relationships

All participants who have undergone CYP2C8 genotyping screening test during screening or baseline will be included in the PG/PK data analysis.

To assess the CYP2C8 pharmacogenomic-pharmacokinetic relationship.

9.1 Variables

For cohort 1-4: PK parameters (i.e. Cmax, AUC0-24 and AUClast) at Day 1 and Day of last treatment (Day 4 or Day 7) versus CYP2C8 genotyping data at screening or baseline- CYP2C8 genotyping data will only be recorded at one time point per subject. For cohort 5: PK parameters (i.e. Cmax and AUClast) at Day 1 (arm 2) or Day 4 (arm 1) versus CYP2C8 genotyping data at screening or baseline- CYP2C8 genotyping data will only be recorded at one time point per subject.

9.1.1 Descriptive analyses

The genotyping CYP2C8 data will be listed by dose cohort and subject. Descriptive summary statistics for raw data will be provided by dose cohort.

Summary statistics will include frequency and proportion (n, %). Multiple comparisons between dose cohorts on log (PK) parameters at Day 1 and Day of last treatment (Day 4 or Day 7) will be performed by ANOVA to compare the plasma PK parameters and the genotypes.

11 Statistical methods for the Data Monitoring Committee (DMC) review of Cohort 5 data

Population for analysis:

- The Full Analysis Set (FAS) will include all participants that received any study drug for a given study period

A cut-off date to produce the outputs for the DMC review will be determined prior to each DMC meeting. All data available up to the cut-off date will be included in the DMC analyses. Since the trial is ongoing, data cleaning may be incomplete at the cut-off for DMC interim analysis.

The outputs will be presented by treatment group based on FAS. For the Cohort 5 secondary and exploratory endpoints assessing changes from baseline to Week 40, the change from baseline to be summarized primarily refers to the change from the baseline prior to BLZ945 drug administration of the initial 12-week treatment period. Additional summaries for change from start of extended treatment (Week 16) will also be included as applicable.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented by treatment arm and visit. Differences from baseline of continuous variables will be presented in the same way. Whenever a figure eases the readability and interpretation of the data compared to a table, the data should be presented using a figure. For example, instead of showing summary statistics of continuous data per timepoint in a table, the relevant summary measures (e.g., mean+/- standard deviation) will be plotted over time by visit and treatment arm.

Participant safety narratives will be provided for SAEs, AEDO, and adverse events of special interest (AESI) as selected by Novartis safety team.

A validated R-shiny app may be used to display a subset of the summaries described below.

The report for the regular monitoring will include presentation of the following data:

- Participant disposition
- Demographics and baseline disease characteristics
- Medical and ALS disease history
- Exposure to study drug
- Concomitant medications
- Adverse events (AEs and SAEs) by System Organ Class (SOC), preferred term (PT), by most frequent PT, and by severity as applicable, AEs leading to treatment discontinuations, deaths and AEs potentially related to risks resulting from BLZ945 treatment (e.g., ECM accumulation, vasculitis)
- Longitudinal changes in lab results, vital signs, and ECG
- Changes in esophageal wall thickness (based on CT scans) and cardiac valve thickness, cardiac valve function and left ventricular ejection fraction (based on echocardiography)
- Suicidality will be reported based on the Columbia Suicide Severity Rating Scale (C-SSRS).

- Time to permanent assisted ventilation or death, whichever occurs first and time to death* from baseline and start of extended treatment to Week 40

  *Vitality will be complemented with information collected quarterly during the 1-year follow-up phone calls

- eDISH (evaluation of drug induced serious hepatoxicity) plots
- Spaghetti plots of liver enzymes plotted in units of ULN