Protocol Title:	A Randomised, Double-Blind, Three-Arm, Single Dose, Parallel Study To Compare the Pharmacokinetics, Safety and Immunogenicity of MB02 (Bevacizumab Biosimilar Drug), US-licenced Avastin® and EU-approved Avastin® in Healthy Male Volunteers
NCT Number:	NCT03293654
Statistical Analysis Plan version date:	Version 2.0, 05 June 2019

STATISTICAL ANALYSIS PLAN

A Randomised, Double-Blind, Three-Arm, Single Dose, Parallel Study to Compare the Pharmacokinetics, Safety, and Immunogenicity of MB02 (Bevacizumab Biosimilar Drug), US-licensed Avastin® and EU-approved Avastin® in Healthy Male Volunteers

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Covance Study Number: 8370738

Clinical Phase 1

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1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical, pharmacokinetic (PK), and immunogenicity analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

Covance approval:

[redacted] Date

Statistician

[redacted] Date

Pharmacokineticist

Sponsor approval:

[redacted] Date

Medical Advisor

2 TABLE OF CONTENTS

3 ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

ADA	anti-drug antibody
ADaM	analysis data model
AE	adverse event
AUC	area under the serum concentration-time curve
$AUC_{(0-\infty)}$	AUC from time zero to infinity
$AUC_{(0-t)}$	AUC from time zero to the time of the last observable concentration
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
BLQ	below the limit of quantification
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL	total body clearance of drug after intravenous administration
C_{max}	maximum observed serum concentration
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
ECG	electrocardiogram
eCRF	electronic Case Report Form
ICH	International Council for Harmonisation
IV	intravenous
k_{el}	Elimination rate constant of the terminal phase
LLOQ	lower limit of quantification
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
QTc	QT correction; QT interval corrected for heart rate
QTcF	QTc calculated using the Fridericia correction

SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
$t_{1/2}$	apparent serum terminal elimination half-life
t_{max}	time of maximum observed serum concentration
V_z	Volume of distribution during the terminal phase after intravenous administration

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 6.0 dated 15 October 2018).

This SAP describes the planned analysis of the safety, tolerability, immunogenicity and PK data from this study. A detailed description of the planned TFLs to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical analyses of safety, tolerability, immunogenicity and PK. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between mAbxience Research S.L. and Covance Early Clinical Biometrics. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be finalised prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalised, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between mAbxience Research S.L. and Covance Early Clinical Biometrics and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Council for Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

5 STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of the study is:

- To investigate and compare the PK profiles of MB02, US-licensed Avastin® (US Avastin®) and EU-approved Avastin® (EU Avastin®) to establish bioequivalence between the 3 study arms.

5.2 Secondary Objectives

The secondary objectives of the study are:

- Evaluation and comparison of derived PK parameters not covered by the primary endpoint for MB02, US Avastin® and EU Avastin®
- To compare the safety profile of MB02, US Avastin® and EU Avastin®
- To compare the immunogenicity of MB02, US Avastin® and EU Avastin®

6 STUDY DESIGN

This will be a Phase 1, double-blind, randomised, parallel-group, single-dose, 3-arm study to investigate and compare the PK, safety and immunogenicity profile of MB02 with US and EU Avastin® in healthy male subjects. A total of 114 subjects will be randomised to one of the following 3 arms in a 1:1:1 ratio:

- Arm 1: MB02 as a 90 minute IV infusion
- Arm 2: Avastin® sourced from the US, as a 90 minute IV infusion
- Arm 3: Avastin® sourced from the EU, as a 90 minute IV infusion.

Thirty-eight subjects will be dosed in each arm.

Subjects will be admitted to the Clinical Research Unit (CRU) on Day -1, and will be confined to the CRU until discharge on Day 8. On Day 1, subjects will receive a single 3 mg/kg IV dose of the study drug. Subjects will return on Days 10, 14, 21, 28, 42, 56, 78 and 100 for nonresidential visits for the collection of PK samples and safety assessments. Immunogenicity samples will be collected on Days 14, 28, 56, and 78.

The total duration of trial participation for each subject (from Screening through to the final visit) is anticipated to be a maximum of 19 weeks. The end of the study is defined as the date of the last subject's last assessment (planned or unplanned).

7 TREATMENTS

The following is a list of the study treatment abbreviations and ordering that will be used in the TFLs.

Study Treatment Name	Abbreviation	Treatment Order on TFLs
3 mg/kg MB02 IV	3 mg/kg MB02 IV	1
3 mg/kg US-licensed Avastin® IV	3 mg/kg US Avastin® IV	2
3 mg/kg EU-approved Avastin® IV	3 mg/kg EU Avastin® IV	3

8 SAMPLE SIZE JUSTIFICATION

Up to 114 subjects will be enrolled in order that 108 complete the study.

A sample size of 36 subjects per arm (108 subjects in total) will provide at least 90% power for all the pairwise comparisons for primary endpoints (AUC and C_{max}) using a percent coefficient

of variation (CV%) of 25% in both PK parameters for the similarity objective if the true ratio is equal to 1.05 or less.

A conservative estimate of CV% was based on a prior MB02 study[3] and information from the public domain[4]. Model-based simulations from a developed population PK literature model, accounting for similarity between bevacizumab sources (EU/US), intrinsic PK altering factors (body weight, sex, serum albumin and alkaline phosphatase), between subject variability and residual variability, showed that a sample size of 90 subjects provided at least 90% probability of concluding PK similarity for the all pairwise comparisons in terms of C_{max} and $AUC_{(0-\infty)}$.

Simulations also showed that the probability of concluding PK similarity in terms of $AUC_{(0-t)}$ is almost the same as $AUC_{(0-\infty)}$.

A maximum of 5% loss of data due to premature discontinuation is expected therefore, the sample size is increased to 114 subjects in total, with 38 subjects per arm.

9 DEFINITION OF ANALYSIS POPULATIONS

The **Safety Population** will include all subjects exposed to MB02 or Avastin® and have at least 1 postdose safety assessment.

The **PK Population** will include all subjects who received the full dose of MB02 or Avastin®, did not have any major protocol deviations, and have an evaluable PK serum concentration-time profile. This population will be used for the primary analysis of PK bioequivalence

All protocol deviations that occur during the study will be considered prior to database lock for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations. Details of subject assignment to the analysis populations will be listed.

The **All Subjects Population** will be consistent with the Safety Population.

10 STATISTICAL METHODOLOGY

10.1 General

Data listings will be provided for the All Subjects Population. Summary statistics and statistical analyses will be performed for subjects included in the relevant analysis populations (Safety/ PK).

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, number of observations (N), and number of subjects (n). For log-normal data (e.g., the PK parameters: areas under the concentration-time curve [AUCs] and maximum observed concentration [C_{max}]), the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will be provided for all subjects up to the point of

withdrawal, with any subjects excluded from the relevant population highlighted. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.4 or higher.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 2.2.0 will be utilised to ensure compliance with CDISC standards.

It is planned that the Sponsor will create a secondary CSR containing only data from MB02 and EU-licensed Avastin therefore to support this all TFLs will be repeated with US-licensed Avastin removed.

10.1.1 Definition of Baseline and Change from Baseline

Baseline for each parameter is defined as the last value measured prior to dosing, including repeat (vital signs and electrocardiograms [ECGs]) and unscheduled (clinical laboratory parameters) readings (see Section 10.1.2 for definitions of repeat and unscheduled readings).

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

10.1.2 Repeat and Unscheduled Readings

Repeat readings occur when the original vital signs or ECG result requires confirmation. Repeat readings are labelled as 'Repeat' in the listings and replace the original readings in all summaries and changes from baseline presentations and calculations. Prior to dosing, all readings taken in addition to the original reading are defined as predose repeats. Postdose repeat readings are defined as readings collected within 15 minutes of the actual time of the original reading.

With the exception of predose results described above, unscheduled readings for vital signs or ECGs are defined as readings collected >15 minutes from the actual time of the original reading. Unscheduled readings are labelled as 'Unscheduled' in the listings. Because unscheduled readings are not associated with any scheduled timepoint, they are excluded from all summaries (with the exception that they may be used as baseline, as stated in Section 10.1.1).

10.2 Demographics and Subject Disposition

The demographic variables age, sex, race, body weight, height, and body mass index will be summarised and listed. Subject disposition will be summarised and listed.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

Serum pharmacokinetic parameters

The following PK parameters will, where possible, be determined from the serum bevacizumab concentration-time profiles obtained following single dosing (using non-compartmental procedures in Phoenix WinNonlin (Certara USA, Inc. Version 6.4, or later):

Parameter	Definition
$AUC_{(0-t)}$	Area under the concentration-time curve from time 0 to the time of last quantifiable concentration
$AUC_{(0-\infty)}$	Area under the concentration-time curve from time 0 extrapolated to infinity
$\%AUC_{extrap}$	Percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
C_{max}	Maximum serum concentration observed
t_{max}	Time of observed maximum serum concentration
$t_{1/2}$	Apparent serum terminal elimination half-life
k_{el}	Elimination rate constant of the terminal phase
CL	Total body clearance of drug after intravenous administration
V_z	Volume of distribution during the terminal phase after intravenous administration

Additional PK parameters may be determined where appropriate.

PK parameters will be calculated for each subject using actual doses and actual sampling times after start of infusion.

Serum concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

C_{max} and t_{max} will be obtained directly from the serum concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

$t_{1/2}$ will be calculated according to the following formula:

$$t_{1/2} = \frac{\ln(2)}{k_{el}}$$

where k_{el} will be calculated by least squares linear regression of the terminal portion of the log-transformed serum concentration-time curve.

The start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point at which there is no systematic deviation from the log-linear decline in serum concentrations.

$AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.

The certificate of testing documents show that although the protein contents of each batch were within the specified range there is variability in the actual protein content between batches and treatments which has the potential to influence the study results, therefore protein corrected $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max} will also be derived for each individual by dividing each parameter by the actual protein content of the product batch that the individual received, according to the table below:

Batch number	Protein content (mg/mL)
17A043	27.2
3240772	24.0
3155155	23.2
B8034H02	23.0
B8027H01	24.2

10.3.2 Criteria for Handling Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

Concentration values that are below the limit of quantification (BLQ) will be set to zero, with defined exceptions as follows.

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.

- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are

considered to be anomalous, they will be set to missing.

- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.

- If a predose concentration is missing on Day 1, these values may be set to zero.

10.3.3 Criteria for Handling Concentrations Above the Limit of Quantification in Pharmacokinetic Analysis

Any samples with concentrations above the upper limit of quantification that could not be reanalysed to determine the exact concentration, will be set as the upper concentration limit of the assay for PK analysis. The concentration and PK parameters will be flagged in the listings but excluded from the summary statistics and will be described in the CSR.

10.3.4 Criteria for the Calculation of an Apparent Terminal Elimination Half-Life

Number of Data Points

- At least three data points will be included in the regression analysis and preferably should not include C_{max}.

Goodness of Fit

- When assessing terminal elimination phases, the R^2 adjusted value will be used as a measure of the goodness of fit of the data points to the determined line.

- Regression-based parameters ($AUC_{(0-\infty)}$, $t_{1/2}$, k_{el}, CL and V_z) will only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.70.

Period of Estimation

- Time period used for the estimation of $t_{1/2}$, where possible, would be recommended to be calculated over at least two half-lives.

- Where an elimination half-life is estimated over a time period of less than two half-lives, it will be flagged in the data listings at the discretion of the pharmacokineticist, and the robustness of the value should be discussed in the study report.

10.3.5 Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive serum concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- For any partial AUC determination (i.e. AUC to common partial area interval), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the pharmacokineticist.

- $AUC_{(0-\infty)}$ values where the percentage extrapolation is less than 20% will be reported. For $AUC_{(0-\infty)}$ and $AUC_{(0-\infty)}$ derived parameters, where the percentage extrapolation is between 20 to 30%, these will be flagged and included in the descriptive statistics. Where the percentage of AUC extrapolation is greater than 30%, $AUC_{(0-\infty)}$ and $AUC_{(0-\infty)}$ derived parameters will be listed but excluded from descriptive statistics.

10.3.6 Anomalous Values

- Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

- On Day 1, positive predose value(s) greater than 5% of C_{max} may be excluded from the summary statistics of PK tables and the PK and statistical analysis as appropriate if there is a valid scientific reason for doing so.

10.4 Presentation of Pharmacokinetic Data

10.4.1 Presentation of Pharmacokinetic Serum Drug Concentration Data

The following rules will be applied if there are values that are BLQ or if there are missing values (e.g., no result [NR]) in a serum concentration data series to be summarized.

- For the calculation of summary statistics, BLQ values will be set to zero.
- If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
- Where there is NR, these will be set to missing.
- If there are less than 3 values in the data series, only the min, max and N will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.
- If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, min and max will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.
- If the value of the arithmetic mean or median is BLQ, these values will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.

10.4.2 Presentation of Pharmacokinetic Parameters

For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.

The AUC values will be set to NC if they have been calculated using fewer than 3 concentrations and/or three concentrations if the last is C_{max}.

10.4.3 Pharmacokinetic Statistical Methodology

Serum Bevacizumab Concentrations

All investigational product serum concentration data and derived PK parameters will be summarised. Individual primary PK parameters will be presented graphically to display the PK of the treatments.

Serum concentrations of bevacizumab will be listed by subject and summarised for each treatment arm and time-point. Descriptive statistics (number of patients, arithmetic mean, SD, CV%, minimum, maximum, median, geometric mean, and geometric CV%) will be calculated for serum concentrations.

In the assessment of bioequivalence MB02 is the test treatment and US Avastin® and EU Avastin® are the reference treatments. MB02 will be considered to be bioequivalent to US Avastin® and EU Avastin® if the 90% confidence intervals (CIs) for the ratios of MB02 relative to US Avastin® and EU Avastin® are completely contained within the interval 0.8000 to 1.2500 for $AUC_{(0-\infty)}$ and C_{max}[5]. The PK population will be used for the analysis.

The PK parameters ($AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max}) will be log-transformed (base e)[6] prior to analysis and will be analysed using an ANCOVA model. The model will include treatment as a fixed effect and body weight as a covariate. An example of the SAS code that will be used (assuming TRTMNT coding is 1= MB02, 2= US Avastin® or EU Avastin®) is as follows:

```
proc mixed data=xxx;
class trtmnt;
model l_pk = trtmnt weight/ ddfm=kr;
estimate 'Test - Ref' trtmnt 1 -1 / cl alpha=0.1;
lsmeans trtmnt;
run;
```

where l_pk is the log-transformed (base e) PK parameter.

For these parameters, least square (LS) means and mean differences will be calculated for MB02 versus US Avastin®, MB02 versus EU Avastin®, and EU Avastin® versus US Avastin®. The residual variance from the model will be used to calculate 90% CI for the differences and these values will be back-transformed to give geometric LS means, a point estimate and 90% CI for the ratio of MB02 relative to US Avastin® and EU Avastin®. This procedure is equivalent to Schuirmann's two one-sided tests[7] at the 0.05 level of significance[7].

Between-subject coefficients of variation (CV_B) will be calculated for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max} based on the log-normal distribution using the following formula:

$$CV_B(\%) = [\exp(mse) - 1]^{½} \times 100$$

where mse is the residual error from the mixed model.

Residual plots will be produced to assess the adequacy of the model.

Sensitivity Analysis

An additional sensitivity analysis will also be performed using the same methodology as the primary analysis but will use the protein adjusted PK parameters as the response variables to assess the impact of the actual protein content on the study results. Analyses may be repeated for subgroups of subjects with or without ADA and de novo ADA formation and any influencing subject demographics as appropriate.

10.5 Safety and Tolerability Assessments

10.5.1 Adverse Events

A baseline sign and symptom is defined as an adverse event (AE) that starts after the subject has provided written informed consent and that resolves prior to the first dosing occasion, or an AE that starts prior to the first dosing occasion and does not increase in severity after dosing. A treatment-emergent AE (TEAE) is defined as an AE that occurs postdose or that is present predose and becomes more severe postdose. AEs will be graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

All AEs will be listed. The TEAEs will be summarised by treatment arm, severity, and relationship to the study drug. The frequency of TEAEs (the number of TEAEs, the number of subjects experiencing a TEAE, and the percentage of subjects experiencing a TEAE) will be summarised by treatment arm, severity grade, and by Medical Dictionary for Regulatory Activities system organ class and preferred term. The percentage of subjects experiencing a TEAE will be compared among the treatments using a fisher's exact test. The summary and frequency TEAE tables will be presented for all causalities and for those TEAEs considered related to the study drug (those that have a relationship of possibly related, probably related, or related). Any severe or serious AEs will be tabulated. For any AEs that change severity ratings the AE will be included only once under the maximum severity rating in the summaries.

Onset times postdose are calculated from the start of infusion.

10.5.2 Clinical Laboratory Parameters

Clinical chemistry, haematology, and coagulation data will be summarised by treatment arm. Changes from baseline will be calculated. In addition, all clinical chemistry, haematology, urinalysis, and coagulation data outside the clinical reference ranges will be listed by parameter and treatment arm.

Values for any clinical chemistry, haematology, urinalysis, and coagulation values outside the clinical reference ranges will be flagged on the individual subject data listings.

Serology data will be listed by subject.

10.5.3 Vital Signs

Vital signs data (including supine blood pressure, supine pulse rate, respiration rate, and oral temperature) will be listed and summarised.

Vital signs values outside the clinical reference ranges will be flagged on the individual subject data listings.

The vital signs data will be summarised by treatment arm, together with changes from baseline. Figures of mean vital signs and mean change from baseline profiles will be presented by treatment arm.

Pulse oximetry data will be listed by subject.

10.5.4 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the QT interval calculated using the QT interval calculated using the Fridericia correction (QTcF), the PR and QT intervals, the QRS duration, and heart rate.

Values for ECG parameters outside the clinical reference ranges will be flagged on the individual subject data listings.

The ECG data will be summarised by treatment arm, together with changes from baseline. Figures of mean ECG data and mean change from baseline profiles will be presented by treatment arm.

10.5.5 Immunogenicity Safety Assessment

Immunogenicity data (overall ADA incidence and titers, and neutralising ADA results) will be listed. A summary of the number and percent of subjects testing positive for ADA and neutralising antibodies before the dose of MB02, EU Avastin®, or US Avastin® (Day -1) and at scheduled postdose assessments will be presented by treatment arm. A summary over all visits will also be presented by treatment, this will be performed separately including and excluding subjects who were positive at baseline. Drug clearance will be presented graphically and numerically by ADA/neutralising ADA status of a subject by treatment. This figure will use the PK population, all other immunogenicity data summaries will be based on the safety population. Select analyses may be repeated for subsets with or without ADA and de novo ADA formation as appropriate.

10.5.6 Other Assessments

All other safety assessments not detailed in this section will be listed but not summarised or statistically analysed.

Medical history data will not be presented.

10.5.7 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11 INTERIM ANALYSES

No interim statistical analyses are planned.

12 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

Protein adjusted primary PK parameters will be calculated and used for a sensitivity analysis.

13 DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, "No serious adverse events occurred for this study."

14 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

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4. Beverly Knight, Danielle Rassam, Shanmei Liao, Reginald Ewesuedo. A phase I pharmacokinetics study comparing PF-06439535 (a potential biosimilar) with bevacizumab in healthy male volunteers. *Cancer Chemother Pharmacol*. 2016; 77: 839-846.

5. Statistical Approaches to Establishing Bioequivalence. Rockville, MD: US Dept of Health and Human Services, Food and Drug Administration; Center for Drug Evaluation and Research (CDER); January 2001.

6. Keene ON. The log transformation is special. Statistics in Medicine 1995; 14: 811 819.

7. Schuirmann DJ. A comparison of the two one sided tests procedure and the power approach for assessing the equivalence of average bioavailability. Journal of Pharmacokinetics and Biopharmaceutics, 1987; 15: 657-680.