Statistical Analysis Plan

Clinical Trial Protocol Identification No.	BD1412-63CEC EMR200763-004
Title:	A randomized, open-label, single dose, 2x2 crossover trial to evaluate the food effect on the bioavailability of a Metformin/Gliclazide fixed combination tablet (1000 mg /30 mg MR) given in fasting and fed conditions to healthy volunteers.
Trial Phase	I
Investigational Medicinal Product(s)	Metformin/ Gliclazide
Clinical Trial Protocol Version	15 November 2017/Version 2.0
Statistical Analysis Plan Author	PPD
Statistical Analysis Plan Date and Version	12 march 2018/Version 1.0
Statistical Analysis Plan Reviewers	PPD, Biostatistics Responsible. PPD, Principal investigator. PPD, Quality Control Responsible PPD, Sanitary Officer. PPD, Quality Assurance Officer. PPD, Bioanalytics Investigator.

1. Signature Page

Statistical Analysis Plan: BD1412-63CEC EMR200763-004

A randomized, open-label, single dose, 2x2 crossover trial to evaluate the food effect on the bioavailability of a Metformin/Gliclazide fixed combination tablet (1000 mg /30 mg MR) given in fasting and fed conditions to healthy volunteers.

PPD

Biostatistics Responsible, PPD

PPD

Medical Responsible, PPD

PPD

Merck KGaA Frankfurter Strasse 250
64293 Darmstadt, Germany

2. Table of Contents

3 List of Abbreviations and Definition of Terms

AE	Adverse Event
AUC	Area under the plasma concentration-time curve
$AUC_{0\rightarrow\infty}$	The AUC from time zero (dosing time) extrapolated to infinity
$AUC_{0\rightarrow t}$	The AUC from time zero (= dosing time) to the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification
$AUC_{extra\%}$	The AUC from time t_{last} extrapolated to infinity given as percentage of $AUC_{0\rightarrow\square}$
BE	Bioequivalence
BMI	Body Mass Index
CI	Confidence Interval
$CL_{/f}$	The apparent total body clearance of drug following extravascular administration.
C_{max}	Maximum observed plasma concentration
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTR	Clinical Trial Report
CTMS	Clinical Trial Management System
CTP	Clinical Trial Protocol
CV	Coefficient of Variation (%)
CYP	Cytochrome P 450
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GeoCV%	Geometric Coefficient of Variation
GeoMean	Geometric Mean
GIR	Glucophage Immediate Release
HR	Hazard ratio
HAV	Hepatitis A Virus

HbA_{1C}	Glycosylated Hemoglobin Type A_{1C}
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
LLOQ	Lower Level of Quantification
Max	Maximum
Mean	Arithmetic mean
Min	Minimum
MedDRA	Medical Dictionary For Regulatory Activities
MRI	Magnetic Resonance Imaging
MSS	Merck Santé s.a.s. in Semoy
N	Number of non-missing observations
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred team
QoL	Quality of Life
SAE	Serious Adverse Event
SASS	Sino-American Shanghai Squibb Pharmaceuticals Ltd
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SEM	Standard Error of the Mean
SOC	System Organ Class
$t_{1/2}$	Apparent terminal half-life
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures

t_{last}	The last sampling time at which the concentration is at or above the lower limit of quantification
t_{max}	The time to reach the maximum observed concentration
TP	Treponema Pallidum
$V_{z/f}$	Apparent volume of distribution during the terminal phase following extravascular administration
λ_z	Terminal elimination rate constant
WHO	World Health Organisation

4 Modification History

Unique Identifier for SAP Version	DATE OF SAP Version	Author	CHANGE DESCRIPTION from the previous version	LEVEL
	March 2019	PPD	New Document	1.0

5 Purpose of the Statistical Analysis Plan

The purpose of this SAP is to document technical and detailed specifications for the final analysis of data collected for protocol BD1412-63CEC EMR200763-004. Results of the analyses described in this SAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this SAP will be included in regulatory submissions or future manuscripts. Any post-hoc.

The SAP is based upon section 9 (Statistical and Pharmacokinetical Analysis) of the trial protocol and is prepared in compliance with ICH E9.

6 Summary of Clinical Trial Features

6.1 Primary Objectives and Endpoints

- To assess the food effect on bioavailability ($AUC_{0-\infty}$, AUC_{0-t} and C_{max}) for Metformin 1000 mg/Gliclazide 30 mg MR, fixed dose combination, tablets, given as single dose in fasting state and with food to healthy volunteers.

6.2 Secondary Objectives and Endpoints

- To estimate pharmacokinetic parameters such as t_{max}, $t_{1/2}$, Vd and CL.
- To compare all experimental treatments' safety.

6.3 Overall Trial Design and Plan

The IMP will be given in fast and fed state. A randomized, open label, single dose, 2 x 2 cross design will be used with a 14-day washout period between 2 study stages. Treatment groups will be balanced, with the same number of subjects, who will be randomized to the dosing sequences (see table below).

Food's effect study			
Sequence	**Period 1**	**Washout period**	**Period 2**
1	Fast		Fed
2	Fed		Fast

All data from participant subjects should be analyzed and included in the statistical analysis, as long as they meet the established criteria.

7 Sample Size

According to the goals for the study treatment regarding postprandial/fasting, pharmacokinetic parameters will be calculated AUC and C_{max} for both analytes, Metformin and Gliclazide. In order to have an accurate and reasonable precision for the estimated ratios, a sufficient amount of subjects will be randomized.

Taking 90 % confidence interval for the postprandial/fasting ratio as a measure for accuracy and assuming an average variation coefficient of 20 % or higher for AUC (AUC0-∞, AUC0-t) and C_{max} for Metformin y Gliclazide, then with 18 evaluable subjects the food effect on pharmacokinetics can be estimated with an accuracy of 12 % or higher. The following ratio will be carried out, being R the estimated ratio and LCL / UCL lower and higher confidence levels for the 90% confidence interval for R:

$0.89 * R \leq LCL < UCL \leq 1{,}12 * R$
An accuracy of 12% or higher will result in an accurate enough description for the food effects. Besides, 18 evaluable subjects are enough to detect a difference among treatments of 18 % or higher with a power of 80 % at least. Taking into account a drop-out rate around 20 %, 22 subjects should be randomized.

8 Overview of Planned Analyses

To determine and compare if the rate and extend of metformin and gliclazide's absorption is affected by food, metformin hydrochloride extended release (XR) 1000 mg/gliclazide 30 mg modified release (MR) in one tablet was assessed in fasting and post-prandial state, depending on the group it was assigned to. Twenty-two (22) subjects were randomized, they were randomly assigned to each of the treatment sequences and given the test formulation in two different periods (fasting and post-prandial state), with a 14-day wash-out period. According to the sampling schedule, plasma was obtained from blood samples collected and using a previously validated

analytical method, the metformin and gliclazide concentrations were determined for each subject and then they were used to determine if bioavailability of the quantified analytes is changed by food. Only twenty-one (21) subject finished the study.

This trial intends to estimate the effect of food on pharmacokinetics. It is not intended to prove or confirm statistically the lack of any food effect.

Therefore, no statistical hypothesis is presented. As primary analysis, a mixed model will be applied for all C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Metformin and C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Gliclazide, of the fixed dose combination metformin /Gliclazide log transformed. With TREATMENT, PERIOD and SEQUENCE as fixed effects, and the SUBJECT (SEQUENCE) as random effect.

Based on the residual error term 90 % confidence intervals will be built for the estimated differences postprandial - fasting, resulting in 90 % confidence intervals for postprandial/fasting ratios following the repeated transformation.

8.1 Interim Analysis

To assess food influence on the study drug assessed, a crossed 2-period and 2-sequence design was used, with a sampling time of 168 hours which allowed to estimate the 90% of the average AUC for the analytes.

The pharmacokinetic analysis for the plasma concentrations was performed using the WinNonlin® software with a non-compartmental model and the use of real times.

The t_{max} and C_{max} values were obtained from the measures taken. The area under the curve of plasma concentration from t_0 (dosing) to the t_n ($AUC_{0\rightarrow t}$), was estimated with the trapezoidal method with lineal interpolation. To determine the area under the curve from the last sampling time to the infinite time ($AUC_{t\rightarrow\infty}$), the last plasma concentration quotient in the clearance rate was determined by lineal regression, using the sampling points from the terminal lineal logarithm which fitted the best to the straight line. The $AUC_{0-\infty}$ was determined adding up the AUC_{0-t} and the $AUC_{t-\infty}$.

The statistical analysis was performed with the WinNonlin® using the least squares with the generalized lineal model (GLM).

The intra-subject Student residual analysis for the pharmacokinetic parameters was performed with Microsoft Excel®.
The following model was used for the analysis:

$$Y_{ijkl} = \mu + S_k + V(S)_{i(k)} + P_j + F_l + e_{ijkl} \text{ …… (Chow \& Liu, 2009)}$$

Where:

Y_{ijkl}	is the response (pharmacokinetic parameter) in the i^{th} volunteer, where *j* is the -th period, and k^{th} sequence with l^{th} treatment.
μ	is the overall mean.
S_k	is the effect of the k^{th} dosing sequence.
$V(S)_{i(k)}$	is the of the i^{th} volunteer in the k^{th} sequence, which is considered a randomized effect.
P_j	is the effect of the j^{th} period (or dosing phase).
F_l	is the effect of the l^{th} treatment or formulation.
e_{ijkl}	is the experimental error, intra-volunteer variability and a randomized effect assumed with normal distribution, zero media, constant variance and independent of the volunteer's effect sequentially nested.

Based on the determination of the average square error and the determination of the geometric means, the classic 90% confidence intervals estimation was made for the test-reference ratio in the previously logarithmic transformed data. Where the test corresponds to the post-prandial conditions and the reference to fasting conditions.

9 Changes to the Planned Analyses in the Clinical Trial Protocol

The statistical methods as described in the protocol were adopted.

There are no changes to the planned analyses.

10 Protocol Deviations and Analysis Sets

10.1 Definition of Protocol Deviations and Analysis Sets

All deviations should be justified with statistical or scientific data and any change to the original statistical plan should be documented, in the study master file and in the pharmacokinetics statistical report as well as in the final study report. Subjects' data will not be replaced. Any missing data will be considered as non-existent data. Likewise, data cannot be removed from the statistical analysis, except in the following events.

- **Research Subjects with Pre-dose Concentrations in the Biological Matrix**

In the event pre-dose concentration is < 5 % of the C_{max} value for a research subject, subject's data can be included without any adjustment to measurement and pharmacokinetic calculations. When pre-dose value is > 5 % of the C_{max}, research subject should be removed from all study bioequivalence assessments.

- **Exclusion of data due to vomit or diarrhea.**

Data from research subjects who experience vomiting and diarrhea throughout the bioequivalence study for immediate release products can be removed from the statistical analysis if vomiting and diarrhea occur before 2 fold the median for t_{max} or 2 fold t_{max} value obtained from the research subject in a given period.

- **Research subject with very low plasma concentrations for study drugs.**

As established by NOM-177-SSA1-2013, research subjects in a cross designed who provide evaluable data for test drug and reference drug, or who do not have evaluable data in the single period of a parallel design, should not be either included in the statistical analysis.

It is considered that a research subject has very low concentrations, if the AUC is lower than 5 % of the geometric means for the reference drug's AUC (it should be calculated without including outliers). Exclusion of data due to this reason will only be accepted prior scientific rationale and review of the case by the COFEPRIS.

11 General Specifications for Statistical Analyses

Pharmacokinetic parameters (non-compartmental analysis) and statistical analysis for determining bioequivalence will be calculated using Phoenix WinNonlin 8.0 software.
The results of this trial will be reported using summary tables, figures, and data listings, as appropriate. All data will be summarized by treatment and/or scheduled time point, as appropriate.

12 Protocol Deviations

12.1 Important Protocol Deviations

Not applicable. No deviation was observed in the study

12.2 Reasons Leading to the Exclusion from an Analysis Set

- **Research Subjects with Pre-dose Concentrations in the Biological Matrix**

In the event pre-dose concentration is less than 5 % of the C_{max} value for a research subject, subject's data can be included. When pre-dose value is greater than 5 % of the C_{max}, research subjects data should be removed from all study of food effect on bioavailability.

- **Exclusion of data due to vomit or diarrhea.**

Data from research subjects who experience vomiting and diarrhea throughout the study for immediate release products can be removed from the statistical analysis if vomiting and diarrhea occur before 2 fold the median for t_{max} or 2 fold t_{max} value obtained from the research subject in a given period.

- **Research subject with very low plasma concentrations for study drugs.**

As established by NOM-177-SSA1-2013, research subjects in a cross designed who provide evaluable data for test drug and reference drug, or who do not have evaluable data in the single period of a parallel design, should not be either included in the statistical analysis.

It is considered that a research subject has very low concentrations, if the AUC is lower than 5 % of the geometric means for the reference drug's AUC (it should be calculated without including

outliers). Exclusion of data due to this reason will only be accepted prior scientific rationale and review of the case by the COFEPRIS.

13 Demographics and Other Baseline Characteristics

Demographic data from each volunteer is shown in table 13.1 and the descriptive statistics for the demographic variables from volunteers recruited in the study are shown in table 13.2. PPD

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13.1 Demographics

Table 13.1. Demographic Variables' Individual Data

Case	Sex	Age	Weight	Height	BMI	Sequence
PPD						

Table 13.2. Demographic Variables' Descriptive Statistics

Statistics	Age (years)	Weight (kg)	Height (m)	BMI (Kg/m^2)
Mean	PPD			
SD				
Median				
25th percentil				
75th percentil				
Minimum				
Maximum				

14 Treatment Compliance and Exposure

All subjects receive the investigational treatment at the pre-specified fixed dosage. Information relating to the extent of exposure is thus contained in the treatment labelling.

15 Endpoint Evaluation

15.1 Primary Endpoint Analyses

The determination of pharmacokinetics parameters were determined using WinNonlin software depending of their own characteristics as follows:

Cmax: is the peak or maximum concentration

AUC_{0-t}: area under de curve computed from time zero to the time of the last positive Y value.

$AUC_{0-\infty}$: area under de curve computed from time zero to extrapolated from infinity.

Ke: First-order rate constant associated with the terminal (log-linear) elimination phase. This is estimated via linear regression of time vs. log concentration.

Primary pharmacokinetics parameters, AUC and C_{max}, were used to estimate the effect of food on pharmacokinetics. It is not intended to prove or confirm statistically the lack of any food effect.

As primary analysis, a mixed model will be applied for all C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Metformin and C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Gliclazide, of the fixed dose combination metformin /Gliclazide log transformed. With TREATMENT, PERIOD and SEQUENCE as fixed effects, and the SUBJECT (SEQUENCE) as random effect.

Based on the residual error term 90 % confidence intervals will be built for the estimated differences postprandial - fasting, resulting in 90 % confidence intervals for postprandial/fasting ratios following the repeated transformation.

Statistical comparisons between treatments A and B, with respect to C_{max}, AUC_{0-t}, and AUC_{∞} of Metformin/Gliclazide, will in each case separate based on a mixed linear model for log transformed (natural log) pharmacokinetic parameter data.

15.2 Bioavailability Statistics

Table 15.2.1 shows the results of the statistic to determine food influence on the metformin's bioavailability. Table 16.1.4 shows the results for gliclazide.

Table 15.2.1. Statistics for the Metformin's Bioequivalence Determination

Parameter	Point Estimate	90% Confidence Interval	Two one-sided T-test		Power	Acceptance Criterion	Meets the Criterion
			P < 80%	P > 125%			
LnC_{max}	PPD						
$LnAUC_{0-t}$							
$LnAUC_{0-\infty}$							

Table 15.2.2. Statistics for the Gliclazide's Bioequivalence Determination

Parameter	Point Estimate	90% Confidence Interval	Two one-sided T-test		Power	Acceptance Criterion	Meets the Criterion
			P < 80%	P > 125%			
LnC_{max}	PPD						
$LnAUC_{0-t}$							
$LnAUC_{0-\infty}$							

As set out in the Mexican Official Standard NOM-177-SSA1-2013, the parameters to establish the conclusion about the bioavailability for the metformin and gliclazide are the C_{max} as absorption rate indicator and the AUC as the absorbed rate amount in this study. The 90% confidence interval results for the mean of the post-prandial/fasting quotients are shown; PPD . PPD

PPD

PPD

15.3 Box and Whiskers plots.

Box and whiskers plots for the parameters used to evaluate the absorption rate and the metformin and gliclazide's bioavailability, respectively, are shown in tables 15.3.1 and 15.3.2. PPD

Table 15.3.1. Box and Whiskers Charts for the Metformin's Pharmacokinetic Parameters

PPD

PPD

Table 15.3.2. Box and Whiskers Charts for the Gliclazide's Pharmacokinetic Parameters

PPD

15.4 Secondary Endpoint Analyses

Average results of the metformin's pharmacokinetic parameters are shown in tables 15.4.1 and 15.4.2, PPD

Table 15.4.1. Metformin's Pharmacokinetic Parameters Results for Fasting Conditions

Metformin Fasting Conditions									
Variable	N	Mean	SD	CV%	Min	Median	Max	Geo Mean	Geo CV%
Cmax	PPD								
Tmax									
Lambda_z									
HL_Lambda_z									
AUClast									
AUCINF_obs									
AUC_%Extrap_obs									
Cl_F_obs									
Vz_F_obs									
MRTINF_obs									

PPD

Table 15.4.2. Metformin's Pharmacokinetic Parameters Results for Fed Conditions

Metformin Fed Conditions									
Variable	N	Mean	SD	CV%	Min	Median	Max	Geo Mean	Geo CV%
Cmax	PPD								
Tmax									
Lambda_z									
HL_Lambda_z									
AUClast									
AUCINF_obs									
AUC_%Extrap_obs									
Cl_F_obs									
Vz_F_obs									
MRTINF_obs									

PPD

Table 15.4.3. Gliclazide's Pharmacokinetic Parameters Results for Fasting Conditions.

Gliclazide Fasting Conditions									
Variable	N	Mean	SD	CV%	Min	Median	Max	Geo Mean	Geo CV%
Cmax	PPD								
Tmax									
Lambda_z									
HL_Lambda_z									
AUClast									
AUCINF_obs									
AUC_%Extrap_obs									
Cl_F_obs									
Vz_F_obs									
MRTINF_obs									

PPD

Table 15.4.4. Gliclazide's Pharmacokinetic Parameters Results for Fed Conditions.

Gliclazide Fed Conditions									
Variable	N	Mean	SD	CV%	Min	Median	Max	Geo Mean	Geo CV%
Cmax	PPD								
Tmax									
Lambda_z									
HL_Lambda_z									
AUClast									
AUCINF_obs									
AUC_%Extrap_obs									
Cl_F_obs									
Vz_F_obs									
MRTINF_obs									

PPD

15.5 Other Endpoint Analyses

Data about plasma concentration versus time for each subject, as well as the descriptive statistics are shown in tables 15.5.1 and 15.5.2 for metformin, with a dosing schedule of the test drug, R for fasting state and T for post-prandial state. Gliclazide's concentrations for both conditions are shown in tables 15.5.1 and 15.5.2.

Table 15.5.1. Individual concentrations table corresponding to metformin in fasting state. n = P volunteers

Form	Volunteer	Time																				
		0.0	0.5	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	10.0	12.0	16.0	24.0	28.0	32.0	48.0	72.0	96.0	120.0	144.0	168.0
PPD																							

Table 15.5.2 Individual concentrations table for metformin in post-prandial state. n = P volunteers

Form	Volunteer	Time																				
		0.0	0.5	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	10.0	12.0	16.0	24.0	28.0	32.0	48.0	72.0	96.0	120.0	144.0	168.0
PPD																							

PPD

PPD

Table 15.5.3. Individual concentrations table for gliclazide in fasting state. n = P volunteers

Form	Volunteer	Time																				
		0.0	0.5	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	10.0	12.0	16.0	24.0	28.0	32.0	48.0	72.0	96.0	120.0	144.0	168.0
PPD																							

Table 15.5.4 Individual concentrations table for gliclazide in post-prandial state. n = 21 volunteers

Form	Volunteer	Time																			
		0.0	0.5	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	10.0	12.0	16.0	24.0	28.0	32.0	48.0	72.0	96.0	120.0	144.0	168.0
PPD																							

PPD

Average values for the metformin and gliclazide's concentration obtained in the study as well as the descriptive statistics are shown in tables 15.5.5 and 15.5.6.

Table 15.5.5. Descriptive Statistics of the Values of the Metformin's Concentration in Biological Fluid

Time	Metformin/Gliclazide fasting contidions						Metformin/Gliclazide fed conditions					
	Mean	Median	Minimum value	Maximum value	Standard deviation	CV%	Mean	Median	Minimum value	Maximum value	Standard deviation	CV%
0.0000	PPD											
0.5000												
1.0000												
2.0000												
3.0000												
4.0000												
5.0000												
6.0000												
7.0000												
8.0000												
10.0000												
12.0000												
16.0000												
24.0000												
28.0000												
32.0000												
48.0000												
72.0000												
96.0000												
120.0000												
144.0000												
168.0000												

Table 15.5.6 Descriptive Statistics of the Values of the Gliclazide's Concentration in Biological Fluid

Time	Metformin/Gliclazide fasting conditions						Metformin/Gliclazide fed conditions					
	Mean	Median	Minimun value	Maximum value	Standard deviation	CV%	Mean	Median	Minimun value	Maximum value	Standard deviation	CV%
0.0000	PPD											
0.5000												
1.0000												
2.0000												
3.0000												
4.0000												
5.0000												
6.0000												
7.0000												
8.0000												
10.0000												
12.0000												
16.0000												
24.0000												
28.0000												
32.0000												
48.0000												
72.0000												
96.0000												
120.0000												
144.0000												
168.0000												

The pharmacokinetic profiles were satisfactorily characterized for metformin and gliclazide. Figures 15.5.1 and 15.5.2 show the average charts in arithmetic and logarithmic scales, respectively, for gliclazide.

Figure 15.5.1. Gliclazide's average concentration versus time chart in an arithmetic scale following the test drugs dosing in fasting and post-prandial state (standard deviation bars)

Figure 15.5.2. Gliclazide's average concentration versus time chart in logarithmic scale following the test drugs dosing in fasting and post-prandial state (standard deviation bars)

16. Estimation of Individual Pharmacokinetic Parameters

Non-compartmental computation of pharmacokinetic parameters was performed using the computer program Phoenix® WinNonlin® version 8.0 (PPD).

The pharmacokinetic analysis was performed with a non-compartmental analysis, using real times following the dosing of the studied drugs. Pharmacokinetic parameters were determined as shown in tables 16.1. and 16.2, which include the individual values and descriptive statistics used for determining food's influence for metformin and gliclazide, respectively.

Table 16.1. Individual Data and Descriptive Statistics for Metformin's Pharmacokinetic Parameters (C_{max} in ng/mL, $AUC_{0\rightarrow t}$ in h*ng/mL and $AUC_{0\rightarrow\infty}$ in h*ng/mL).

Volunteer	Period		Sequence	$C_{máx}$				ABC_{0-t}				$ABC_{0-\infty}$			
	Form			Form		T/R	Ln(T/R)	Form		T/R	Ln(T/R)	Form		T/R	Ln(T/R)
	R	T		R	T			R	T			R	T		
PPD															

Table 16.2. Individual Data and Descriptive Statistics for Gliclazide's Pharmacokinetic Parameters (C_{max} in ng/mL, $AUC_{0\rightarrow t}$ in h*ng/mL and $AUC_{0\rightarrow \infty}$ in h*ng/mL).

Volunteer	Period		Secuencia	$C_{máx}$				ABC_{0-t}				$ABC_{0-\infty}$			
	Form			Form		T/R	Ln(T/R)	Form		T/R	Ln(T/R)	Form		T/R	Ln(T/R)
	R	T		R	T			R	T			R	T		
PPD															

The Phoenix WinNonlin NCA Core Output is provided in a separate listing.

17 Safety Evaluation

According to the Mexican Official Standard, NOM-177-SSA1-2013, there are several statistical tests to identify extreme values. Most of them start by calculating the student residual absolute value. Likewise, it is stated that "since studies are generally crossed designed, the most important extreme values is the extreme value for the subject".

An adequate method for estimating extreme values allows increasing reliability of the study conclusion. An analysis to identify outliers (extreme) values based on the student residual estimation among subjects will be performed using Bear software (current) for R environment.

Criterion: extreme values are those data which degree is higher than ± 2 standardized residuals intra-subject.

17.1 Pharmacokinetic Parameters' Outliers

Outliers analysis' results by means of the intra-subject Student residual values calculation was performed according to the Mexican Official Standard NOM-177-SSA1-2013, which states that the possible outliers will be those which exceed the criterion of ± 2 Student residual values. Values exceeding that limit for metformin and gliclazide are shown in tables 17.1. and 17.2. Student residual values vs. the assessed pharmacokinetic parameter for metformin are shown in figures 17.0.1 to 17.0.3. Student residual values for gliclazide are shown in charts 17.0.4 to 17.0.6.

Table 17.1. Volunteers Exceeding the Criterion of ± 2 Student Residual Values for Metformin

Pharmacokinetic Parameter	Volunteer	Student Residual Value
LnC_{max}	PPD	
$LnAUC_{0-t}$		
$LnAUC_{0-\infty}$		

Table 17.2. Volunteers Exceeding the Criterion of ± 2 Student Residual Values for Gliclazide

Pharmacokinetic Parameter	Volunteer	Student Residual Value
LnC_{max}	PPD	
$LnAUC_{0-t}$		
$LnAUC_{0-\infty}$		

Figure 17.0.1. Intra-subject Student Residual Values Chart for the Metformin's Pharmacokinetic Parameter Ln C_{max}

Figure 17.0.2. Intra-subject Student Residual Values Chart for the Metformin's Pharmacokinetic Parameter Ln AUC_{0-t}

Figure 17.0.3. Intra-subject Student Residual Values Chart for the Metformin's Pharmacokinetic Parameter Ln $AUC_{0-\infty}$

Figure 17.0.4. Intra-subject Student Residual Values Chart for the Gliclazide's Pharmacokinetic Parameter Ln C_{max}

Figure 17.0.5. Intra-subject Student Residual Values Chart for the Gliclazide's Pharmacokinetic Parameter Ln AUC_{0-t}

Figure 17.0.6. Intra-subject Student Residual Values Chart for the Gliclazide's Pharmacokinetic Parameter Ln $AUC_{0-\infty}$

To establish if the determined outliers influenced the result, a statistical exercise was performed to remove volunteer 1 from the gliclazide's analysis. It was seen that the statistic's results on food influence do not change; therefore, they are not influential outliers.
Volunteer 1, identified as outlier did not show any incident in the clinical study process or in the analytical stage. Each area conducted the investigation of the previously mentioned cases and did not find any responsible cause for the results abnormality. Thus, there is no evidence supporting their removal from the statistical analysis.

18. Adverse Events

All the information related with clinical results is included in clinical inform

19 References

- Chow S.S, Liu JP. (2009). Design and Analysis of Bioavailability and Bioequivalence Studies. 3rd edition. US: CRC Press.
- Mexican Official Standard NOM-177-SSA1-2013 which sets out the tests and procedures to prove that a drug is interchangeable, requirements for the authorized third parties performing interchangeability tests; requirements for the conduct biocomparability studies, requirements for authorized third parties, research centers and hospitals conducting biocomparability tests.

20 Appendices

- Quality Assurance Report.
- Individual Concentrations
- Winnonlin Core Outputs