Statistical Analysis Plan

Clinical Trial Protocol Identification No.	BD1412-62CEC EMR200763-003
Title:	Randomized, Open label, Single Dose, 4-treatments, 4-periods, Crossover design (4 x 4) Study to evaluate the Bioequivalence and Secondarily Drug - Drug Interaction of Fixed Combination of Metformin Tablets 1000 mg/Gliclazide 30 mg MR, Compared with the Co-administration of Individual Tablets and Individual Administration of Each single tablet (Metformin 1000 mg XR and Gliclazide 30 mg MR) in Healthy Volunteers.
Trial Phase	I
Investigational Medicinal Product(s)	Metformin/ Gliclazide
Clinical Trial Protocol Version	2 October 2017/Version 1.0
Statistical Analysis Plan Author	PPD
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Statistical Analysis Plan Reviewers	PPD, Biostatistics Responsible. PPD, Principal investigator. PPD, Quality Control Responsible PPD, Sanitary Officer. PPD, Quality Assurance Officer. PPD, Bioanalytics Investigator.

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1. Signature Page

Statistical Analysis Plan: BD1412-62CEC EMR200763-003

Randomized, Open label, Single Dose, 4-treatments, 4-periods, Crossover design (4 x 4) Study to evaluate the Bioequivalence and Secondarily Drug - Drug Interaction of Fixed Combination of Metformin Tablets 1000 mg/Gliclazide 30 mg MR, Compared with the Co-administration of Individual Tablets and Individual Administration of Each single tablet (Metformin 1000 mg XR and Gliclazide 30 mg MR) in Healthy Volunteers.

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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 BD1412-62CEC EMR200763-003. 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 demonstrate bioequivalence of the fixed combination of Metformin tablets 1000 mg XR plus Gliclazide 30 mg MR compared to the co-administration of the individual tablets of Metformin 1000 mg XR and Gliclazide 30 mg MR, given as single dose to healthy volunteers in fasting state. Primary endpoints will be AUC0-t, AUC0-∞ and Cmax for Metformin and Gliclazide.
- To demonstrate the lack of an effect of Gliclazide on the PK of Metformin by comparing the Metformin PK following administration of the fixed combination tablet Metformin/Gliclazide and Metformin alone (AUC0-t, AUC0-∞ and Cmax of Metformin).
- To demonstrate the absence of an effect of Metformin on the PK of Gliclazide by comparing the Gliclazide PK following administration of the fixed combination tablet Metformin/Gliclazide and Gliclazide alone (AUC0-t, AUC0-∞ and Cmax of Gliclazide).

6.2 Secondary Objectives and Endpoints

- The secondary endpoints variable are volume of distribution Ke, half-life elimination, clearance, and median residence time all these parameters will be presented only for informative reasons for both medications.
- To compare the safety and tolerability of all the experimental treatments.

6.3 Overall Trial Design and Plan

This randomized, open-label, single dose, four-treatment, four period crossover design (4x4) trial with a 14-day wash-out period along 4 study stages will investigate the bioequivalence (primary endpoints are AUC0-t, AUC0-∞ or Cmax for Metformin and Gliclazide) of a Metformin/Gliclazide fixed combination tablet (1000 mg /30 mg MR) compared with the co-administration of the individual tablets (Metformin 1000 mg and Gliclazide 30 mg MR) and the drug-drug interaction between the Metformin/Gliclazide fixed combination and the administration of each single tablet, administered in fasted condition in 40 healthy volunteers. Secondarily, safety and tolerability will be also investigated in every case.

The subjects will be randomized to one of the 4 treatment sequences (see table below). Ten subjects will be randomized to each treatment sequence with a minimum proportion of 30% for each sex in each treatment sequence.

Sequence	Period 1		Period 2		Period 3		Period 4
1	Fixed combination	**Wash-out period**	Metformin + Gliclazide	**Wash-out period**	Metformin	**Wash-out period**	Gliclazide
2	Metformin + Gliclazide		Gliclazide		Fixed combination		Metformin
3	Metformin		Fixed combination		Gliclazide		Metformin + Gliclazide
4	Gliclazide		Metformin		Metformin + Gliclazide		Fixed combination

7 Sample Size

The sample size estimation is based on the CV intrasubject variability of both drugs. Because the pharmacokinetic and drug-drug interaction, evaluates changes in the bioavailability, the propose is the use the same determination for both aims.

The sample size is determined by the primary endpoint with the greatest variability under fasting conditions, AUC0-t of Metformin (CV=23%). Assuming a mean treatment ratio of 0.95, and aiming at a power of 90% for the individual test, alpha=0.05 one-sided, 32 evaluable subjects are sufficient to demonstrate bioequivalence in the first step. The same arguments can be applied to the second step: Test absence of an effect of Gliclazide on the PK of Metformin, whereas the power for the third test is close to 100% with 32 subjects, due to the low variability of Gliclazide PK. Therefore, the overall power is still greater than 80% with 32 evaluable subjects. Considering a drop-out rate of approximately 20%, 40 subjects should be randomized.

According to NOM-177-SSA1-2013, this sample determination was realized with Chow & Wang (2001) equation

$$n \geq \left[t_{(\alpha,2n-2)} + t_{(\beta,2n-2)}\right]^2 \cdot \left(\frac{CV_{intra}}{\ln 0.8 - \ln \theta}\right)^2$$

Where:
t(alfa, 2n-2) and t(beta, 2n-2) considered the error alfa and beta respectively
CVintra: intra subject variability for crossover (or replicate crossover) study.
Tetha: 0.95: the target ratio in average BA between the two formulations expressed in percentage of the average reference
0.8: the least statistical power to detect (1-Power) differences between the Test and the Reference formulation (in this case the power expected is 90%)

8 Overview of Planned Analyses

Statistical analysis and analysis of PK parameters will be performed using Phoenix WinNonlin software Version 6.3 (PPD).

Descriptive statistical methods will be used to summarize demographic characteristics, pharmacokinetics parameters and adverse events. After the data base closing

Individual plasma concentration-time will be tabulated and plotted. Primary pharmacokinetics parameters, AUC and Cmax, will be tabulated and plotted by subject. Likewise, differences and odd ratios for test/reference will be tabulated for each subject for those parameters. Plasma concentration - time graphs will be made using arithmetic and semi-logarithmic scale. All de calculations will be determinated in concordance with NOM-177-SSA1-2013

The following sequential testing of a priori ordered hypotheses will be applied, as shown below. Bioequivalence test methodology will be used in all 3 steps:

1. Test bioequivalence of fixed combination and separate tablets
2. Test absence of an effect of Gliclazide on the PK of Metformin
3. Test absence of an effect of Metformin on the PK of Gliclazide

8.1 Interim Analysis

Bioequivalence in step1:

A mixed model will be applied to log-transformed Cmax, AUC0-t and AUC0-∞ (both analytes) with treatment, period and sequence as fixed effects, and subject (sequence) as a random effect. Based on the residual error term 90% confidence intervals will be computed for the estimated

differences Test – Reference, resulting in 90% confidence intervals for the Test/Reference ratios after back-transformation.

Drug-drug interaction in steps 2 and 3:

A mixed model will be applied to log-transformed Cmax, AUC0-t and AUC0-∞ (one analyte) with treatment as fixed effect, and subject as a random effect. Based on the residual error term 90% confidence intervals will be computed for the estimated differences Test – Reference, resulting in 90% confidence intervals for the Test/Reference ratios after back-transformation.

1. Bioequivalence will be concluded, if all six 90% CIs for all six primary endpoints reside within the acceptance range [0.80 – 1.25]
2. Absence of an effect of Gliclazide on the PK of Metformin will be concluded, if all three 90% CIs for Metformin endpoints reside within the range [0.80 – 1.25]
3. Absence of an effect of Metformin on the PK of Gliclazide will be concluded, if all three 90% CIs for Gliclazide endpoints reside within the range [0.80 – 1.25]

Additionally, the primary endpoints will be descriptively analyzed and graphical displays (Box-whiskers-plots) will be prepared.
Statistical model in the variance analysis of mixed effects should be applied for log-transformed parameters Cmax, AUC0-t and AUC0-∞ (one analyte) with TREATMENT as fixed effect and SUBJECT as randomized effect. Based on residual errors, confidence interval of 90 % will be built for estimated differences for test - reference, resulting in a confidence interval of 90 % for the test/reference ratio following transformation.

Using minimum mean squares for AUC and Cmax, two-side t test will be performed (Schuirmann's test) by constructing confidence intervals of 90 % for test/reference ratios. If and only if intervals are within interval (80, 125), bioequivalence will be proven for both drugs.

Bioequivalence is concluded if 6 confidence intervals for the analytes are included into the bioequivalence limits.

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

13.1 Demographics

Table 13.1. Demographic Variables' Individual Data

Case	Sex	Age	Weight	Height	BMI	Sequence
PPD						

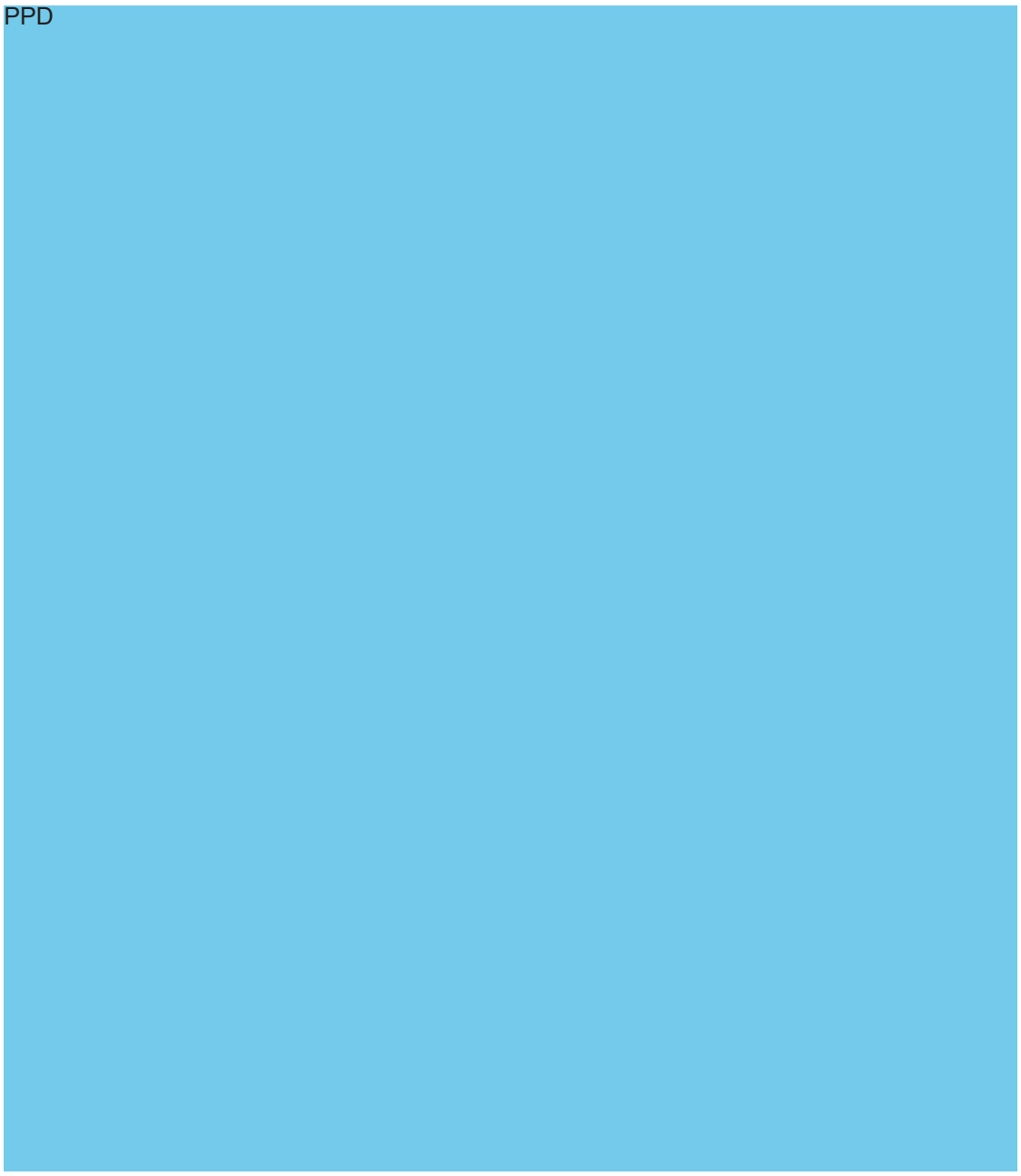


Table 13.2. Demographic Variables' Descriptive Statistics

Statistics	Age (years)	Weight (kg)	Height (m)	BMI (Kg/m^2)
Mean	PPD			
SD				
Median				

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.

To demonstrate bioequivalence of the fixed combination of Metformin tablets 1000 mg XR plus Gliclazide 30 mg MR compared to the co-administration of the individual tablets of Metformin 1000 mg XR and Gliclazide 30 mg MR, given as single dose to healthy volunteers in fasting state. Primary endpoints will be AUC0-t, AUC0-∞ and Cmax for Metformin and Gliclazide.

To demonstrate the lack of an effect of Gliclazide on the PK of Metformin by comparing the Metformin PK following administration of the fixed combination tablet Metformin/Gliclazide and Metformin alone (AUC0-t, AUC0-∞ and Cmax of Metformin).

To demonstrate the absence of an effect of Metformin on the PK of Gliclazide by comparing the Gliclazide PK following administration of the fixed combination tablet Metformin/Gliclazide and Gliclazide alone (AUC0-t, AUC0-∞ and Cmax of Gliclazide).

15.2 Bioavailability Statistics

In tables 15.2.1 and 15.2.2, pharmacokinetic equivalence statistical results are shown for the metformin's logarithmically transformed pharmacokinetic data, taking *Dabex® XR + Diamicron MR® (*B formulation) as reference drug. In tables 15.2.3 and 15.2.4, pharmacokinetic equivalence

statistical results are shown for the metformin's logarithmically transformed pharmacokinetic data, taking *Dabex® XR (*C formulation) as the reference drug.

Table 15.2.1. Statistics for the Metformin's Pharmacokinetic Equivalence Determination. The Assessed Products are: Metformin-Gliclazide vs Dabex® XR + Diamicron MR®. (Dabex® XR as reference)

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

Table 15.2.2. Statistics for the Metformin's Pharmacokinetic Equivalence Determination. The Assessed Products are: Metformin-Gliclazide vs Dabex® XR.

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

Table 15.2.3. Statistics for the Metformin's Pharmacokinetic Equivalence Determination. The Assessed Products are: Dabex® XR vs Dabex® XR + Diamicron MR®. (Dabex® XR alone as reference)

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

Table 15.2.4. Statistics for the Gliclazide's Pharmacokinetic Equivalence Determination. The Assessed Products are: Metformin-Gliclazide vs Dabex® XR + Diamicron MR®. (Diamicron MR® as reference)

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

Table 15.2.5. Statistics for the Gliclazide's Pharmacokinetic Equivalence Determination. The Assessed Products are: Metformin-Gliclazide vs Diamicron MR®.

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

Table 15.2.6. Statistics for the Gliclazide's Pharmacokinetic Equivalence Determination. The Assessed Products are: Diamicron MR® vs Dabex® XR + Diamicron MR®. (Diamicron MR® alone as reference)

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

As set for in the Mexican Official Standard, NOM-177-SSA1-2013, the parameters to be assessed in this study to establish the conclusion about the potential bioequivalence of drugs are C_{max} as indicative of the rate of absorption and the AUC as indicative of the absorbed amount. Results of bio-inequivalence are shown. PPD

Table 15.2.1 shows the results of the evaluation of the metformin and gliclazide given concomitantly versus the test formulation containing both drugs. PPD

In table 15.2.3, when the metformin reference drug is administered versus the concomitant administration of the reference drugs (metformin + gliclazide), aPPD

Tables 15.2.4, 15.2.5, and 15.2.6 show the gliclazide's pharmacokinetic equivalence results in all assessments made; PPD

The estimated statistical power was greater than 80 % for all the parameters assessed, which implies a good certainty to determine a bioequivalence and that the sample size was appropriate.

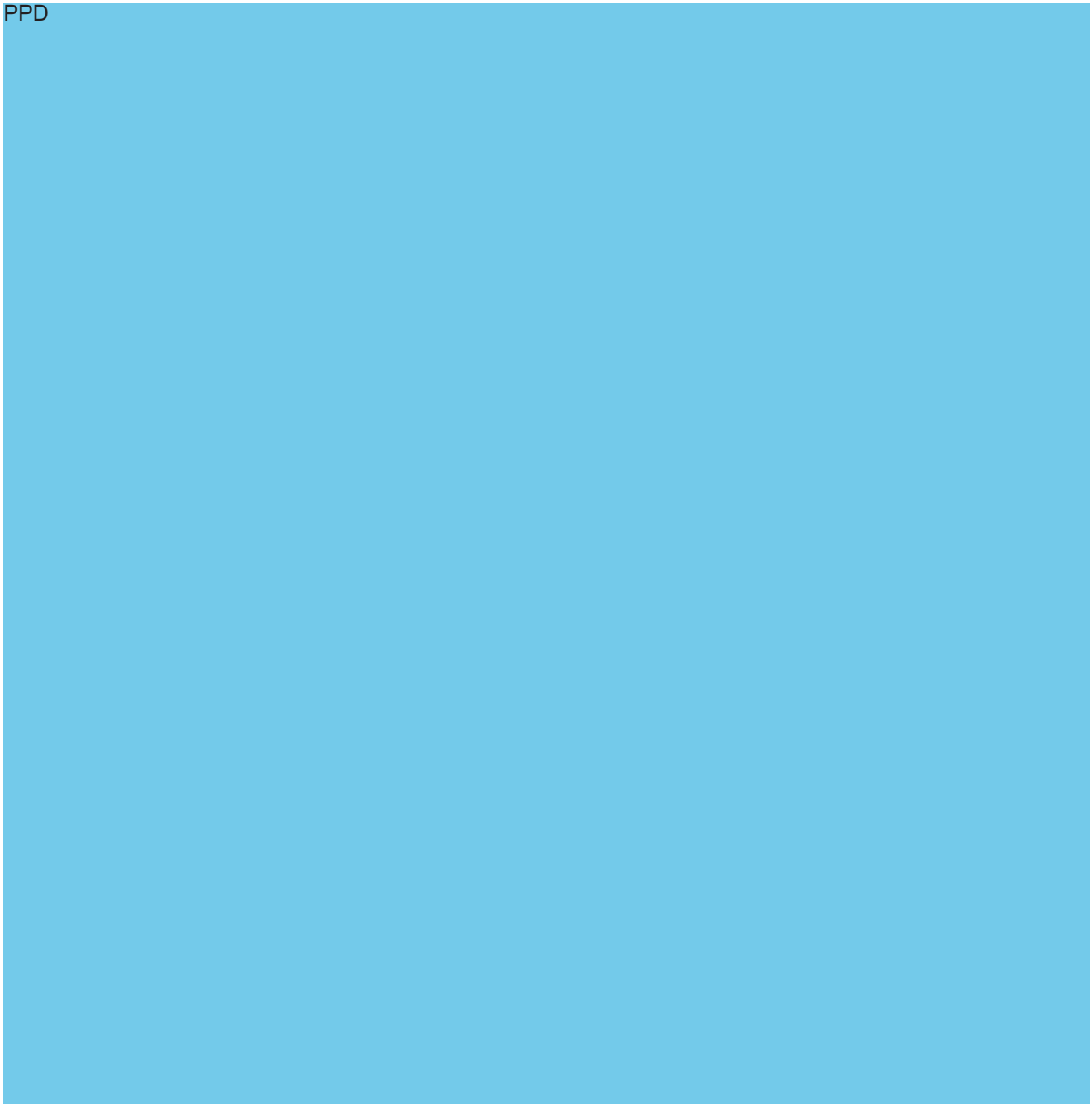
PPD

15.3 Box and Whiskers plots.

In tables 15.3.1 and 15.3.2, box and whiskers plots corresponding to the parameters used to assess the absorption and bioavailability for metformin and gliclazide, respectively, are shown. PPD

Figure 15.3.1 Box and Whiskers Plot for the Metformin's Pharmacokinetic Parameters

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



PPD

[redacted]

15.4 Secondary Endpoint Analyses

Average results of the metformin's pharmacokinetic parameters are shown in tables 15.4.1 for test formulation, 15.4.2 for metformin + gliclazide reference formulations and 15.4.3 for metformin reference. In these tables are shown the pharmacokinetics parameters determined for metformin.

Table 15.4.1. Metformin's Pharmacokinetic Parameters Results for test formulation

Variable	Metformin-Gliclazide								
	N	Mean	SD	CV%	Min	Max	Median	Geometric Mean	CV% Geometric Mean
AUC_%Extrap_obs	PPD								
AUCINF_obs									
AUClast									
Cl_F_pred									
Cmax									
HL_Lambda_z									
MRTINF_obs									
Tmax									
Vz_F_pred									

Table 15.4.2. Metformin's Pharmacokinetic Parameters Results for concomitant reference administration

Variable	Dabex® XR + Diamicron MR®								
	N	Mean	SD	CV%	Min	Max	Median	Geometric Mean	CV% Geometric Mean
AUC_%Extrap_obs	PPD								
AUCINF_obs									
AUClast									
Cl_F_pred									
Cmax									
HL_Lambda_z									
MRTINF_obs									
Tmax									
Vz_F_pred									

Table 15.4.3. Metformin's Pharmacokinetic Parameters Results for reference administration alone

Variable	Dabex® XR								
	N	Mean	SD	CV%	Min	Max	Median	Geometric Mean	CV% Geometric Mean
AUC_%Extrap_obs	PPD								
AUCINF_obs									
AUClast									
Cl_F_pred									
Cmax									
HL_Lambda_z									
MRTINF_obs									
Tmax									
Vz_F_pred									

Average results of the gliclazide's pharmacokinetic parameters are shown in tables 15.4.4 for test formulation, 15.4.5 for metformin + gliclazide reference formulations and 15.4.6 for gliclazide reference. In these tables are shown the pharmacokinetics parameters determined for metformin.

Table 15.4.4. Gliclazide's Pharmacokinetic Parameters Results for test formulation

Variable	Metformin-Gliclazide								
	N	Mean	SD	CV%	Min	Median	Max	Geometric Mean	CV% Geometric Mean
AUC_%Extrap_obs	PPD								
AUCINF_obs									
AUClast									
Cl_F_pred									
Cmax									
HL_Lambda_z									
MRTINF_obs									
Tmax									
Vz_F_pred									

Table 15.4.5. Glicalzide's Pharmacokinetic Parameters Results for concomitant reference administration

Variable	Dabex® XR + Diamicron MR®								
	N	Mean	SD	CV%	Min	Median	Max	Geometric Mean	CV% Geometric Mean
AUC_%Extrap_obs	PPD								
AUCINF_obs									
AUClast									
Cl_F_pred									
Cmax									
HL_Lambda_z									
MRTINF_obs									
Tmax									
Vz_F_pred									

Table 15.4.6. Gliclazide's Pharmacokinetic Parameters Results for reference administration alone

Variable	Diamicron MR®								
	N	Mean	SD	CV%	Min	Median	Max	Geometric Mean	CV% Geometric Mean
AUC_%Extrap_obs	PPD								
AUCINF_obs									
AUClast									
Cl_F_pred									
Cmax									
HL_Lambda_z									
MRTINF_obs									
Tmax									
Vz_F_pred									

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 for metformin test formulation, 15.5.2 for metformin + gliclazide reference formulations concomitant administration and 15.5.3 for metformin reference alone administration.

Table 15.5.1. Individual concentrations table corresponding to metformin-gliclazide test formulation. n = P volunteers

Form	Volunteer	Time																				
		0.0000	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
PPD																							

Table 15.5.2 Individual concentrations table for metformin + gliclazide, reference formulation, concomitant administration. n = P volunteers

Form	Volunteer	Time																				
		0.0000	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
PPD																							

Table 15.5.3 Individual concentrations table for metformin reference formulation, alone administration. n = P volunteers

Form	Volunteer	Time																					
		0.0000	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
PPD																							

PPD

Data about plasma concentration versus time for each subject, as well as the descriptive statistics are shown in tables 15.5.4 for gliclazide test formulation, 15.5.5 for metformin + gliclazide reference formulations concomitant administration and 15.5.6 for gliclazide reference alone administration.

Table 15.5.4. Individual concentrations table corresponding to metformin-gliclazide test formulation. n = P volunteers

Form	Volunteer	Time																					
		0.0000	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
PPD																							

Table 15.5.5 Individual concentrations table for metformin + gliclazide, reference formulation, concomitant administration. n = P volunteers

Form	Volunteer	Time																				
		0.0000	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
PPD																							

-: Sample not delivered.

Table 15.5.6 Individual concentrations table for metformin reference formulation, alone administration. n = P volunteers

Form	Volunteer	Time																				
		0.0000	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
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 15.5.7 and 15.5.8.

Table 15.5.7. Descriptive Statistics of the Values of the Metformin's Concentration in Biological Fluid

Time	Metformin-Gliclazide						Dabex® XR + Diamicron MR®						Dabex® XR					
	Mean	Median	Minimum value	Maximum value	Standar deviation	CV%	Mean	Median	Minimum value	Maximum value	Standar deviation	CV%	Mean	Median	Minimum value	Maximum value	Standar deviation	CV%
PPD																		

Table 15.5.8 Descriptive Statistics of the Values of the Gliclazide's Concentration in Biological Fluid

Time	Metformin-Gliclazide						Debex® XR + Diamicron MR®						Debex® XR					
	Mean	Median	Minimum value	Maximum value	Standar deviation	CV%	Mean	Median	Minimum value	Maximum value	Standar deviation	CV%	Mean	Median	Minimum value	Maximum value	Standar deviation	CV%
PPD																		

PPD

Figures 15.5.1 and 15.5.2 show the average charts in arithmetic and logarithmic scales, respectively, for gliclazide are shown in figures 15.5.3 and 15.5.4 in arithmetic and logarithmic scales.

Figure 15.5.1. Metformin's average concentration versus time chart in an arithmetic scale following the test and reference administration (standard deviation bars)

Figure 15.5.2. Metformin's average concentration versus time chart in logarithmic scale following the test and reference administration (standard deviation bars)

Figure 15.5.1. Metformin's average concentration versus time chart in an arithmetic scale following the test and reference administration (standard deviation bars)

Figure 15.5.2. Metformin's average concentration versus time chart in logarithmic scale following the test and reference administration (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 bioequivalence and drug-drug interaction, between the active ingredients, 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_{max}							AUC_{0-t}							$AUC_{0-\infty}$						
	Form				Form			A/B	Ln(A/B)	A/C	Ln(A/C)	Form			A/B	Ln(A/B)	A/C	Ln(A/C)	Form			A/B	Ln(A/B)	A/C	Ln(A/C)
	A	B	C		A	B	C					A	B	C					A	B	C				
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			Sequence	C_{max}							AUC_{0-t}							$AUC_{0-\infty}$						
	Form				Form			A/B	Ln(A/B)	A/C	Ln(A/C)	Form			A/B	Ln(A/B)	A/C	Ln(A/C)	Form			A/B	Ln(A/B)	A/C	Ln(A/C)
	A	B	C		A	B	C					A	B	C					A	B	C				
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 determination is by means of the intra-subject student residuals calculation according to the Mexican Official Standard, NOM-177-SSA1-2013; therefore, the potential outliers are those which exceed the criterion of ± 2 student residuals. In this study, outliers were determined according to Rasheed A. et al 2011, who states the statistical methodology to determine the outliers for the designs of more than two formulations, by means of the Andrew's curve. In figures 17.1.1, 17.1.2 and 17.1.3 the assessed pharmacokinetic parameters plots to determine the metformin's pharmacokinetic equivalence are shown, and in figures 17.1.4, 17.1.5 and 17.1.6 the assessed pharmacokinetic parameters plots to determine the gliclazide's pharmacokinetic equivalence are shown.

Figure 17.1.1. Intra-subject Student Residuals Plot for the Metformin's Pharmacokinetic Parameter Ln C_{max}

Figure 17.1.2. Intra-subject Student Residuals Plot for the Metformin's Pharmacokinetic Parameter Ln AUC_{0-t}

Figure 17.1.3. Intra-subject Student Residuals Plot for the Metformin's Pharmacokinetic Parameter Ln $AUC_{0-\infty}$

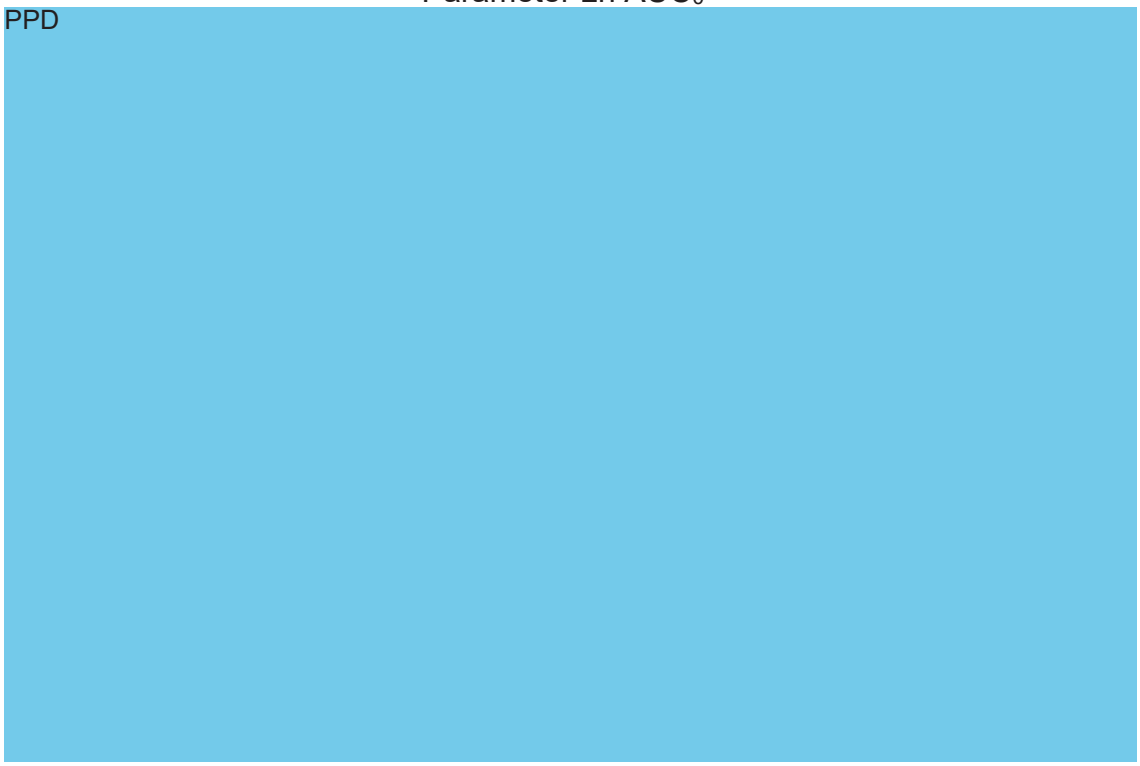


Figure 17.1.4. Intra-subject Student Residuals Plot for the Gliclazide's Pharmacokinetic Parameter Ln C_{max}

Figure 17.1.5. Intra-subject Student Residuals Plot for the Gliclazide's Pharmacokinetic Parameter Ln AUC_{0-t}

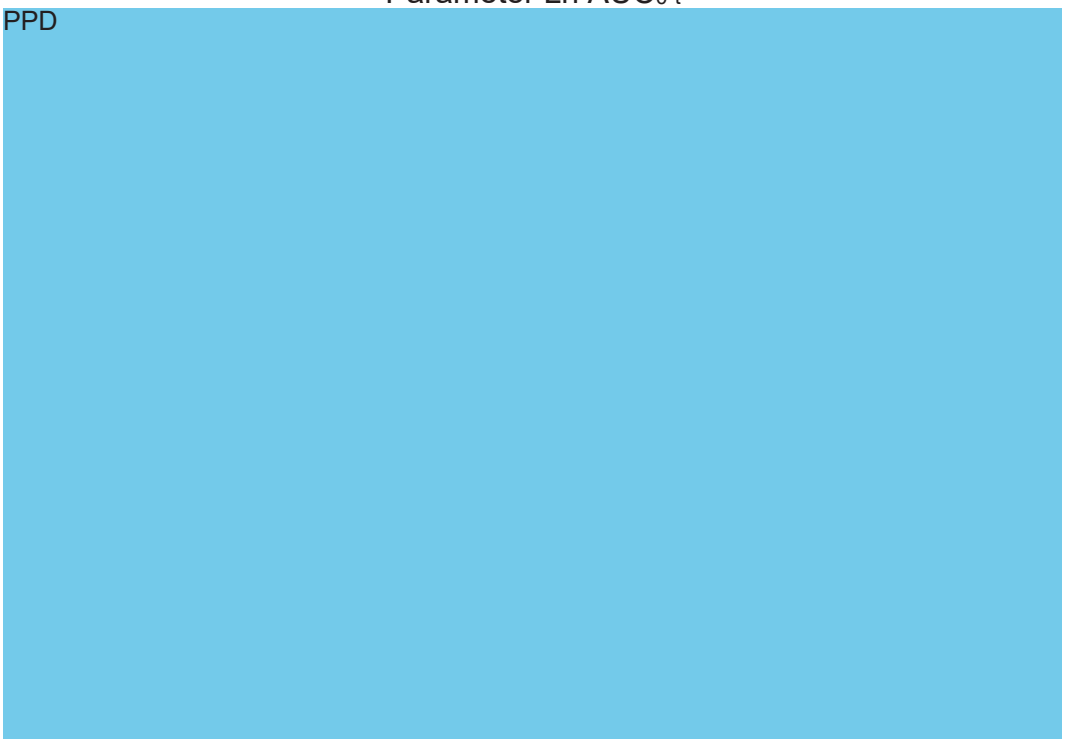


Figure 17.1.6. Intra-subject Student Residuals Plot for the Gliclazide's Pharmacokinetic Parameter Ln $AUC_{0-\infty}$

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