2. STUDY SUMMARY

Name of Sponsor/Company: Institut de Recherches Internationales Servier (I.R.I.S.) **Name of finished product:** Gliclazide MR 120 mg tablets **Name of active ingredient:** Gliclazide MR	**Individual Study Table referring to Part ___ of Dossier** Volume: Page:	*(For authorities use only)*

Title of Study:	A Single-Dose, Randomized, Open-Label, Crossover, Exploratory Bioavailability Study in Healthy Volunteers of Two Formulations of Gliclazide MR Tablets 120 mg (I.R.I.S.) and Two Diamicron® MR Tablets 60 mg (I.R.I.S.) under Fasting and Fed Conditions and Oral Solution of 60 mg Gliclazide (I.R.I.S.) under Fasting Conditions.
Principal Investigator:	Marlene Fonseca, MD [redacted]
Study Center:	BlueClinical Phase I BlueClinical – Investigação e Desenvolvimento em Saúde, Lda. Hospital da Prelada, 0 Floor and 3rd Floor Rua de Sarmento de Beires, 153, 4250-449 Porto, Portugal. Phone: +351 220 959 020, Fax: +351 223 200 699, phase1@blueclinical.pt
Publications:	None.
Dates of Clinical Part:	07NOV2023 (first screening) to 20DEC2023 (last completion).
Phase of Development:	Phase I (Comparative Bioavailability / Pharmacokinetics Study)
Objectives:	*Primary objectives*: 1. To evaluate the pharmacokinetics in plasma and the relative bioavailability of Gliclazide modified release (MR) 120 mg tablets (I.R.I.S.), developed as Test A and Test B with three different releasing rates (slow, medium, and fast release rate), and two Diamicron® MR 60 mg tablets (I.R.I.S.), after a single oral administration under fasting conditions. 2. To evaluate the pharmacokinetics in plasma and the relative bioavailability of Gliclazide MR 120 mg tablets (I.R.I.S.) developed as Test A and Test B with a medium releasing rate, and two Diamicron® MR 60 mg tablets (I.R.I.S.) under fed conditions. *Secondary objectives*: 1. To support the development of a level A *In Vitro-In Vivo* Correlation (IVIVC) for Gliclazide MR 120 mg tablets. 2. To assess the safety and tolerability of the investigational products.

Endpoints:	*Primary endpoints*: Gliclazide pharmacokinetic parameters: maximum observed plasma concentration (C_{max}), area under the plasma concentration *versus* time curve (AUC) from time of dosing (t=0h) to the time of last measurable concentration (AUC_{0-t}), and AUC from time of dosing (t=0h) extrapolated to infinity ($AUC_{0-\infty}$). *Secondary endpoints*: 1. Gliclazide pharmacokinetic parameters: time of occurrence of C_{max} (t_{max}); lag time (t_{lag}); last quantifiable concentration (C_{last}); time of C_{last} (t_{last}); residual area or percentage of extrapolated part of $AUC_{0-\infty}$ ($\%AUC_{extrap}$); apparent terminal elimination rate constant (λ_z); and apparent terminal elimination half-life ($t_{½}$). 2. Safety and Tolerability: Safety was evaluated through the assessment of adverse events (AEs), laboratory tests, vital signs, physical examination, and electrocardiogram (ECG).
Methodology:	Single-center, single-dose, open-label, laboratory-blinded, randomized: – Group 1 and Group 2: five-treatment, three-sequence, five-period crossover exploratory study under fasting conditions. – Group 3: three-treatment, two-sequence, three-period crossover exploratory study under fed conditions. Doses of investigational and auxiliary medicinal products were separated by a washout interval of at least 7 days.
Number of Subjects (Planned and Analyzed):	Planned: To enroll 68 subjects. Actual: Enrolled = 68 subjects. *Group 1: 24 subjects (7 women and 17 men)* Completed Period 1: 24 subjects; Completed Period 2: 24 subjects; Completed Period 3: 23 subjects; Completed Period 4: 23 subjects; Completed Period 5: 23 subjects. Analyzed for safety: 24 subjects; analyzed for pharmacokinetics: 24 subjects; analyzed for comparative bioavailability: 23 subjects. *Group 2: 24 subjects (10 women and 14 men)* Completed Period 1: 24 subjects; Completed Period 2: 24 subjects; Completed Period 3: 24 subjects; Completed Period 4: 24 subjects; Completed Period 5: 24 subjects. Analyzed for safety: 24 subjects; analyzed for pharmacokinetics: 24 subjects; analyzed for comparative bioavailability: 24 subjects. *Group 3: 20 subjects (7 women and 13 men)* Completed Period 1: 20 subjects; Completed Period 2: 20 subjects; Completed Period 3: 20 subjects. Analyzed for safety: 20 subjects; analyzed for pharmacokinetics: 20 subjects; analyzed for comparative bioavailability: 20 subjects.
Diagnosis and Main Selection Criteria:	Healthy male and nonpregnant female volunteers, with age ≥18 and ≤50 years, body mass index (BMI) ≥18.5 and ≤30.0 kg/m^2,

	and non-smokers or ex-smokers were selected according to the defined inclusion and exclusion criteria. The healthy status was determined by pre-study medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory tests (including blood glucose level).
Test Product A, Dose and Mode of Administration, Batch Number:	*Test Product A1 (Test A1):* Gliclazide MR 120 mg tablets – fast release rate Dosage form/Route of administration: tablets/oral Regimen: single dose of 120 mg Batch no.: L0084387 (retest date: 24JAN2024) *Test Product A2 (Test A2):* Gliclazide MR 120 mg tablets – medium release rate Dosage form/Route of administration: tablets/oral Regimen: single dose of 120 mg Batch no.: L0084385 (retest date: 24JAN2024) *Test Product A3 (Test A3):* Gliclazide MR 120 mg tablets – slow release rate Dosage form/Route of administration: tablets/oral Regimen: single dose of 120 mg Batch no.: L0084395 (retest date: 24JAN2024)
Test Product B, Dose and Mode of Administration, Batch Number:	*Test Product B1 (Test B1):* Gliclazide MR 120 mg tablets – fast release rate Dosage form/Route of administration: tablets/oral Regimen: single dose of 120 mg Batch no.: L0084428 (retest date: 02FEB2024) *Test Product B2 (Test B2):* Gliclazide MR 120 mg tablets – medium release rate Dosage form/Route of administration: tablets/oral Regimen: single dose of 120 mg Batch no.: L0084425 (retest date: 02FEB2024) *Test Product B3 (Test B3):* Gliclazide MR 120 mg tablets – slow release rate Dosage form/Route of administration: tablets/oral Regimen: single dose of 120 mg Batch no.: L0084420 (retest date: 02FEB2024)
Reference Product, Dose and Mode of Administration, Batch Number:	Reference product: Diamicron® MR 60 mg tablets Dosage form/Route of administration: tablets/oral Regimen: single dose of 2 x 60 mg Batch no.: 6078404 (expiry date: APR2026)
Auxiliary Medicinal Products:	Auxiliary Medicinal Product 1 (AxMP1): Gliclazide for the extemporaneous preparation of the 60 mg/60 mL oral solution; manufactured by Les Laboratoires Servier Industrie, Gidy, France for the development of a level A IVIVC.

	Auxiliary Medicinal Product 2 (AxMP2): Dextrose 5% solution for infusion. Auxiliary Medicinal Product 3 (AxMP3): Dextrose 10% solution for infusion.
Duration of Treatment and Subject Confinement:	Duration of clinical trial (per participant): Screening: Day -28 to Day -1 (up to 28 days). Treatment periods: In each study period, participants were confined at the clinical research facilities from at least 11 hours before dosing until after the 36-hour post-dose procedures. Then, they left the unit and returned for the 48-, 72- and 96-hour post-dose assessments. Washout period between treatment administrations: 7 calendar days minimum. *Group 1 and Group 2 – Fasting Conditions* Treatment periods 1 to 5: Total study duration of up to 63 days (including Screening). *Group 3 – Fed Conditions* Treatment periods 1 to 3: Total study duration of up to 48 days (including Screening).
Criteria for Evaluation	
Pharmacokinetics:	Plasma concentrations of gliclazide were measured to determine the following primary pharmacokinetic endpoints: – C_{max} – AUC_{0-t} – $AUC_{0-\infty}$
Safety:	Safety was evaluated through the assessment of AEs, ECG, physical examination, vital signs, blood glucose tests, and clinical laboratory tests. Blood glucose value < 3.9 mmol/L (70 mg/dL), asymptomatic or with symptoms suggestive of hypoglycaemia, was treated with IV dextrose administration and was to be reported as an AE.
Statistical Methods:	For pharmacokinetic analysis: Pharmacokinetic evaluation of gliclazide statistical analyses was performed using Phoenix® WinNonlin® 8.3, by using a non-compartmental approach with a *ln*-linear terminal phase assumption. The comparisons of interest were: – Group 1 (Fasting Conditions): - Test A1 *versus* Reference, - Test A2 *versus* Reference, - Test A3 *versus* Reference. – Group 2 (Fasting Conditions): - Test B1 *versus* Reference, - Test B2 *versus* Reference, - Test B3 *versus* Reference.

	– Group 3 (Fed Conditions): - Test A2 *versus* Reference, - Test B2 *versus* Reference. For each comparison of interest, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of gliclazide were evaluated statistically using analysis of variance (ANOVA) after logarithmic transformation with fixed effects for Sequence, Subject within Sequence, and Treatment being included in the model. Least-squares (LS) means, LS treatment difference, and 90% confidence interval (CI) for the treatment differences on the log-scale were obtained for each of the pharmacokinetic parameters. The results were back-transformed to the original scale by exponentiation to provide LS geometric means, point estimate of the geometric mean ratio (GMR) and its corresponding 90% CI. As a secondary objective, an IVIVC model was developed for gliclazide MR 120 mg (Level A to be reached in priority), to describe the relationship between *in vitro* dissolution and the *in vivo* release of gliclazide. The IVIVC report constitutes a separate report from this Clinical Study Report (CSR) of this *in vivo* human trial. *For evaluation of safety and tolerability:* All safety assessments were summarized with descriptive statistics where appropriate and presented in the data listing. Observed values and change from baseline were summarized by treatment as continuous variables, if applicable.
Summary – Conclusions	
Study Population – Outcomes:	A total of 152 subjects were screened for participation. Among them, 68 were enrolled in the study, and 67 were randomly assigned to one of the treatment sequences and 67 completed the study. One (1) subject prematurely discontinued from the study (Group 1) due to failure to meet admission criteria on Period 3. The mean age (± SD) of the safety population was of 33 ± 6.5 years, and the mean BMI of 24.6 ± 2.9 kg/m^2; approximately 65% of them were male. All the protocol deviations reported for subjects included in the analysis were judged to have no significant impact on the study's pharmacokinetic results or subjects' safety.
Pharmacokinetic Results:	*Group 1 – Fasting Conditions (Test A)* Arithmetic mean (A_{mean}) gliclazide plasma concentration *versus* time profiles following administration of Test A1, Test A2, Test A3, Reference, and AxMP1 products are displayed below, in linear and semi-logarithmic scales.

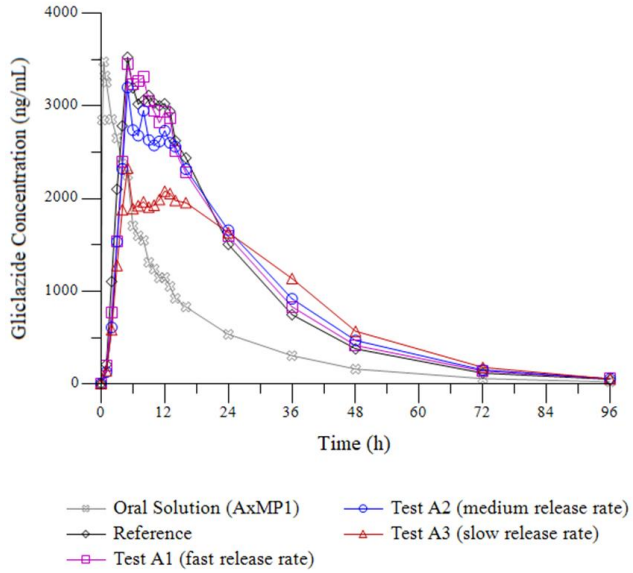

Figure A.1 - Gliclazide: Arithmetic mean plasma concentration *versus* time profiles following administration on group 1 of test a1, test a2, test a3, and reference products and oral solution, under fasting conditions – linear scale

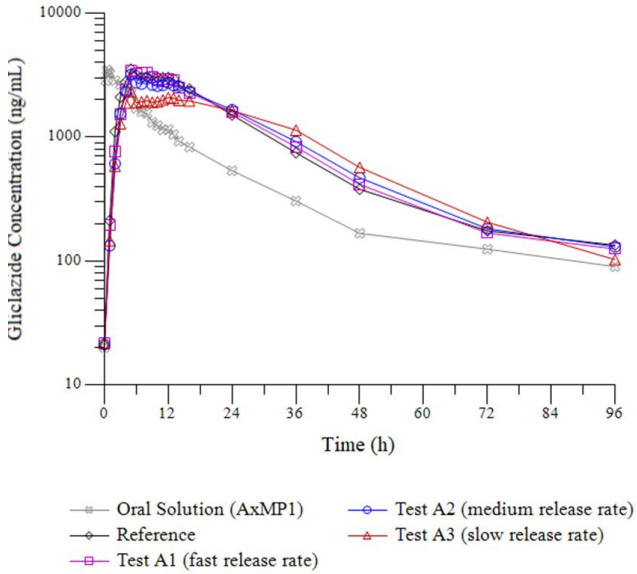

Figure A.2 - Gliclazide: Arithmetic mean plasma concentration *versus* time profiles following administration on group 1 of test a1, test a2, test a3, and reference products and oral solution, under fasting conditions – semi-logarithmic scale

The summary statistics of gliclazide pharmacokinetic parameters following administration of Test A1, Test A2, Test A3, and Reference products under fasting conditions were as follows:

Parameter (unit)	Test A1 (n=23)	Test A2 (n=23)	Test A3 (n=23)	Reference (n=24)
C_{max} (ng/mL)	4079.81 (25.9%)	3663.52 (32.2%)	2767.65 (29.0%)	4181.42 (31.2%)
t_{max} (h)	7.00 (5.00 - 16.00)	5.00 (3.00 - 24.00)	8.00 (4.00 - 36.00)	6.00 (3.00 - 16.02)
t_{lag} (h)	0.00 (0.00 - 2.00)	0.00 (0.00 - 1.00)	0.00 (0.00 - 1.00)	0.00 (0.00 - 1.00)
C_{last} (ng/mL)	85.02 (84.6%)	88.58 (76.2%)	86.19 (63.6%)	79.12 (103.9%)
t_{last} (h)	72.00 (71.90 - 96.30)	72.00 (72.00 - 96.20)	96.00 (71.93 - 96.18)	72.01 (72.00 - 96.22)
AUC_{0-t} (ng.h/mL)	83089.72 (34.8%)	82722.79 (29.5%)	77215.92 (31.6%)	82350.28 (35.2%)
$AUC_{0-\infty}$ (ng h/mL)	85298.71 (36.6%)	84865.01 (30.8%)	79104.27 (32.1%)	84309.04 (37.3%)
$\%AUC_{extrap}$ (%)	2.09 (97.3%)	2.15 (88.0%)	2.17 (76.8%)	1.78 (104.6%)
λ_z (1/h)	0.055 (29.2%)	0.057 (31.5%)	0.057 (28.7%)	0.060 (32.1%)
$t_{1/2}$ (h)	14.02 (39.6%)	13.51 (37.0%)	13.40 (33.9%)	12.97 (39.1%)

n - Number of Participants
Values are arithmetic mean (A_{mean}) with coefficient of variation (CV%) between parenthesis
t_{max}, t_{lag} and t_{last} values are median with range between parentheses
Test A1 – one gliclazide MR 120 mg tablet (fast release rate);
Test A2 – one gliclazide MR 120 mg tablet (medium release rate);
Test A3 – one gliclazide MR 120 mg tablet (slow release rate);
Reference – two Diamicron® MR 60 mg tablets.

The total intra-subject coefficient of variation (ISCV%), Test-to-Reference GMR, and the corresponding 90% CI for gliclazide C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were as follows:

Comparison	Parameter	ISCV%	GMR (%)	90% CI
Test A1 *versus* Reference	C_{max}	20.2	98.17	88.72 – 108.63
	AUC_{0-t}	6.5	99.19	96.00 – 102.48
	$AUC_{0-\infty}$	6.6	99.44	96.20 – 102.80
Test A2 *versus* Reference	C_{max}	22.6	86.93	77.66 – 97.31
	AUC_{0-t}	7.3	100.01	96.39 – 103.76
	$AUC_{0-\infty}$	7.5	100.33	96.60 – 104.20
Test A3 *versus* Reference	C_{max}	19.0	66.28	60.26 – 72.90
	AUC_{0-t}	12.1	92.24	86.78 – 98.05
	$AUC_{0-\infty}$	12.0	92.55	87.11 – 98.34

Test A1 – one gliclazide MR 120 mg tablet (fast release rate);
Test A2 – one gliclazide MR 120 mg tablet (medium release rate);
Test A3 – one gliclazide MR 120 mg tablet (slow release rate);
Reference – two Diamicron® MR 60 mg tablets.

For Test A1 *versus* Reference comparison, the Test A1-to-Reference GMR and corresponding 90% CI are within the acceptance range of 80.00% to 125.00%, for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.
For Test A2 *versus* Reference comparison, the pharmacokinetic results show that the Test A2-to-Reference GMR for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are all within the bioequivalence acceptance range of 80.00% to 125.00%. However, the lower limit of the corresponding 90% CI for C_{max} is below the lower limit of the acceptance range. For AUC_{0-t} and $AUC_{0-\infty}$, the corresponding 90% CIs are within the acceptance bioequivalence range of 80.00% to 125.00%.
For Test A3 *versus* Reference comparison, the Test A3-to-Reference GMR and corresponding 90% CI are outside the acceptance range of 80.00% to 125.00% for C_{max}. For AUC_{0-t} and $AUC_{0-\infty}$, the Test A3-to-Reference GMR and corresponding 90% CI are within the acceptance range.

Group 2 – Fasting Conditions (Test B)

A_{mean} gliclazide plasma concentration *versus* time profiles following administration of Test B1, Test B2, Test B3, Reference, and AxMP1 products are displayed below, in linear and semi-logarithmic scales.

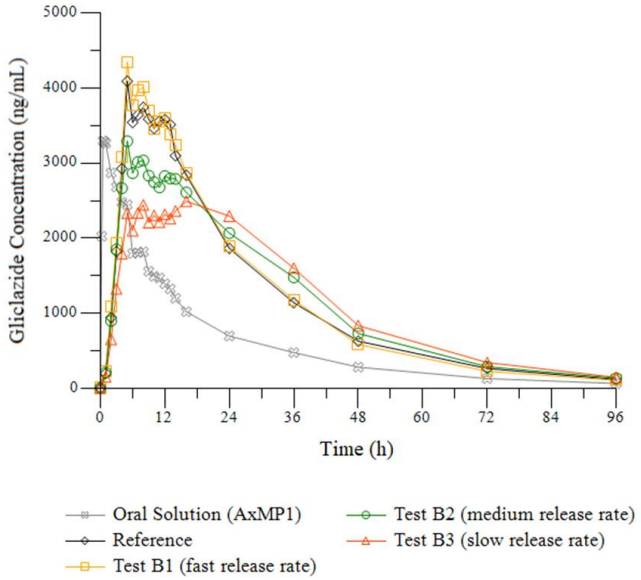

Figure B.1 - Gliclazide: Arithmetic mean plasma concentration *versus* time profiles following administration on group 2 of test b1, test b2, test b3, and reference products and oral solution, under fasting conditions – linear scale

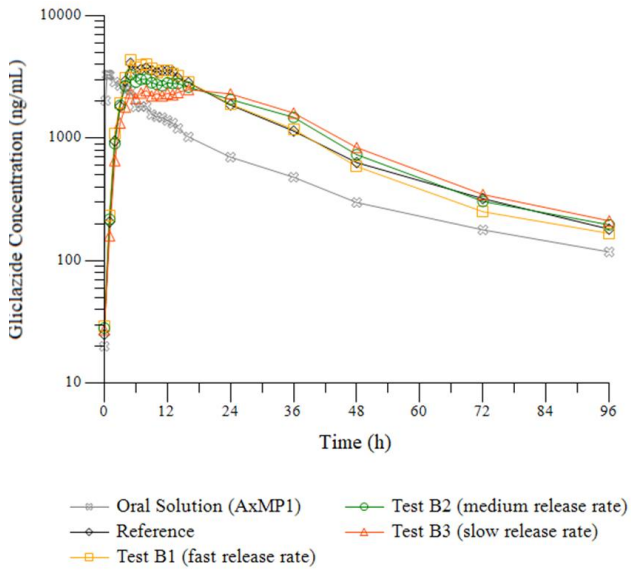

Figure B.2 - Gliclazide: Arithmetic mean plasma concentration *versus* time profiles following administration on group 2 of test b1, test b2, test b3, and reference products and oral solution, under fasting conditions – semi-logarithmic scale

The summary statistics of gliclazide pharmacokinetic parameters following administration of Test B1, Test B2, Test B3, and Reference products, under fasting conditions, were as follows:

Parameter (unit)	Test B1 (n=24)	Test B2 (n=24)	Test B3 (n=24)	Reference (n=24)
C_{max} (ng/mL)	4766.87 (30.5%)	3674.52 (33.4%)	2991.53 (27.9%)	4478.64 (27.6%)
t_{max} (h)	5.00 (4.00 - 14.00)	9.50 (4.00 - 24.00)	13.00 (5.00 - 36.00)	6.00 (5.00 - 13.00)
t_{lag} (h)	0.00 (0.00 - 2.00)	0.00 (0.00 - 1.00)	0.00 (0.00 - 1.00)	0.00 (0.00 - 2.00)
C_{last} (ng/mL)	127.75 (78.6%)	156.06 (82.0%)	166.83 (77.8%)	135.45 (97.1%)
t_{last} (h)	107695.09 (38.6%)	107022.67 (39.7%)	105362.37 (39.5%)	107015.53 (42.1%)
AUC_{0-t} (ng h/mL)	111337.31 (40.0%)	111568.12 (41.8%)	110100.86 (41.2%)	111094.82 (44.4%)
$AUC_{0-\infty}$ (ng h/mL)	2.74 (73.7%)	3.41 (65.5%)	3.66 (70.4%)	2.96 (82.1%)
$\%AUC_{extrap}$ (%)	0.048 (36.4%)	0.045 (38.2%)	0.046 (36.4%)	0.048 (40.2%)
λ_z (1/h)	16.39 (33.9%)	17.18 (32.6%)	16.74 (32.1%)	16.68 (36.7%)
$t_{1/2}$ (h)	107695.09 (38.6%)	107022.67 (39.7%)	105362.37 (39.5%)	107015.53 (42.1%)

n - Number of Participants
Values are arithmetic mean (A_{mean}) with coefficient of variation (CV%) between parenthesis
t_{max}, t_{lag} and t_{last} values are median with range between parentheses
Test B1 – one gliclazide MR 120 mg tablet (fast release rate);
Test B2 – one gliclazide MR 120 mg tablet (medium release rate);
Test B3 – one gliclazide MR 120 mg tablet (slow release rate);
Reference – two Diamicron® MR 60 mg tablets.

The total ISCV%, Test-to-Reference GMR, and the corresponding 90% CI for gliclazide C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were as follows:

Comparison	Parameter	ISCV%	GMR (%)	90% CI
Test B1 *versus* Reference	C_{max}	15.5	106.15	98.37 – 114.54
	AUC_{0-t}	6.0	101.47	98.50 – 104.53
	$AUC_{0-\infty}$	6.2	101.23	98.17 – 104.39
Test B2 *versus* Reference	C_{max}	15.1	81.43	75.61 – 87.70
	AUC_{0-t}	5.3	100.54	97.96 – 103.19
	$AUC_{0-\infty}$	5.4	101.00	98.34 – 103.74
Test B3 *versus* Reference	C_{max}	15.1	66.78	61.99 – 71.95
	AUC_{0-t}	8.0	98.63	94.80 – 102.63
	$AUC_{0-\infty}$	8.1	99.36	95.45 – 103.43

Test B1 – one gliclazide MR 120 mg tablet (fast release rate);
Test B2 – one gliclazide MR 120 mg tablet (medium release rate);
Test B3 – one gliclazide MR 120 mg tablet (slow release rate);
Reference – two Diamicron® MR 60 mg tablets.

For Test B1 *versus* Reference comparison, the Test B1-to-Reference GMR and corresponding 90% CI are within the acceptance range of 80.00% to 125.00%, for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.
For Test B2 *versus* Reference comparison, the pharmacokinetic results show that the Test B2-to-Reference GMR for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are all within the bioequivalence acceptance range of 80.00% to 125.00%. However, the lower limit of the corresponding 90% CI for C_{max} is below the lower limit of the acceptance range. For AUC_{0-t} and $AUC_{0-\infty}$, the corresponding 90% CIs are within the acceptance bioequivalence range of 80.00% to 125.00%.
For Test B3 *versus* Reference comparison, the Test B3-to-Reference GMR and corresponding 90% CI are outside the acceptance range of 80.00% to 125.00% for C_{max}. For AUC_{0-t} and $AUC_{0-\infty}$, the Test B3-to-Reference GMR and corresponding 90% CI are within the acceptance range.

Group 3 – Fed Conditions (Test A2 and Test B2)

A_{mean} gliclazide plasma concentration *versus* time profiles

following administration of Test A2, Test B2, and Reference products are displayed below, in linear and semi-logarithmic scales.

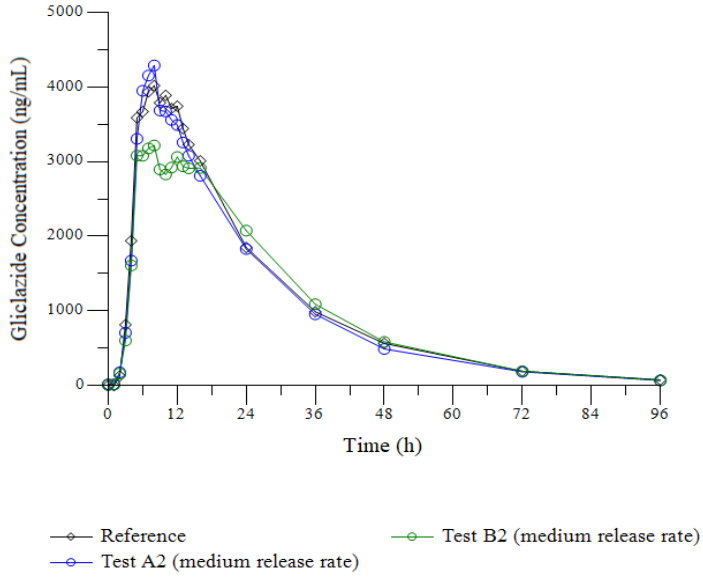

Figure C.1 - Gliclazide: Arithmetic Mean Plasma Concentration *Versus* Time Profiles Following Administration on Group 3 of Test A2, Test B2, and Reference Products, Under Fed Conditions – Linear Scale

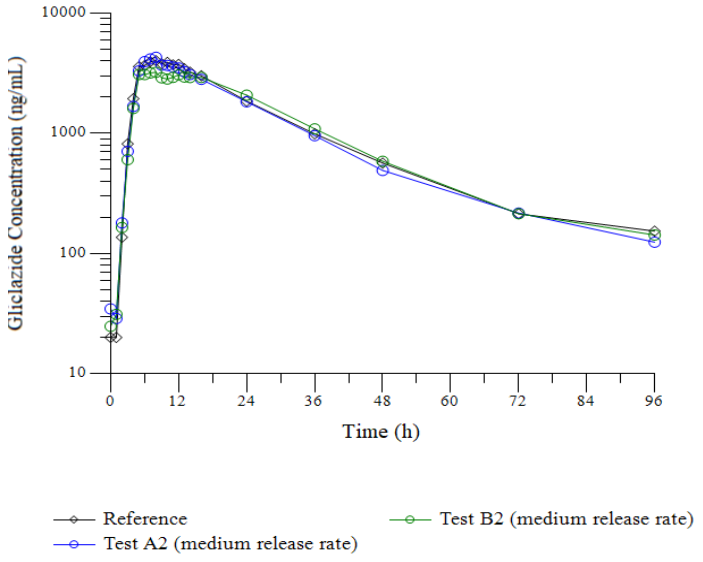

Figure C.2 - Gliclazide: Arithmetic Mean Plasma Concentration *Versus* Time Profiles Following Administration on Group 3 of Test A2, Test B2, and Reference Products, Under Fed Conditions – Semi-Logarithmic Scale

The summary statistics of gliclazide pharmacokinetic parameters following administration of Test A2, Test B2, and Reference products, under fed conditions, were as follows:

Parameter (unit)	Test A2 (n=20)	Test B2 (n=20)	Reference (n=20)
C_{max} (ng/mL)	4680.08 (21.1%)	3808.57 (25.5%)	4743.15 (17.8%)
t_{max} (h)	7.00 (5.00 - 12.00)	8.00 (5.00 - 14.00)	7.00 (5.00 - 13.00)
t_{lag} (h)	1.00 (0.00 - 2.00)	1.00 (0.00 - 2.00)	1.00 (1.00 - 3.00)
C_{last} (ng/mL)	101.63 (90.8%)	103.54 (88.3%)	109.66 (100.7%)
t_{last} (h)	96.00 (72.00 - 96.45)	84.02 (72.00 - 96.27)	84.09 (71.60 - 96.17)
AUC_{0-t} (ng.h/mL)	96052.78 (39.2%)	95642.57 (39.4%)	99926.97 (40.0%)
$AUC_{0-\infty}$ (ng.h/mL)	98744.75 (41.2%)	98064.46 (41.0%)	102827.75 (42.6%)
$\%AUC_{extrap}$ (%)	2.19 (84.3%)	2.03 (71.4%)	2.14 (92.0%)
λ_z (1/h)	0.051 (29.9%)	0.054 (26.3%)	0.053 (27.8%)
$t_{1/2}$ (h)	14.91 (33.5%)	13.76 (26.7%)	14.22 (33.8%)

n - Number of Participants
Values are arithmetic mean (A_{mean}) with coefficient of variation (CV%) between parenthesis
t_{max}, t_{lag} and t_{last} values are median with range between parentheses
Test A2 – one gliclazide MR 120 mg tablet (medium release rate);
Test B2 – one gliclazide MR 120 mg tablet (medium release rate);
Reference – two Diamicron® MR 60 mg tablets.

The total ISCV%, Test-to-Reference GMR, and the corresponding 90% CI for gliclazide C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were as follows:

Comparison	Parameter	ISCV%	GMR (%)	90% CI
Test A2 *versus* Reference	C_{max}	13.6	98.14	91.12 – 105.71
	AUC_{0-t}	5.5	95.88	93.04 – 98.81
	$AUC_{0-\infty}$	5.4	95.93	93.13 – 98.81
Test B2 *versus* Reference	C_{max}	12.3	79.00	73.86 – 84.49
	AUC_{0-t}	6.0	95.79	92.68 – 99.00
	$AUC_{0-\infty}$	5.9	95.66	92.64 – 98.78

Test A2 – one gliclazide MR 120 mg tablet (medium release rate);
Test B2 – one gliclazide MR 120 mg tablet (medium release rate);
Reference – two Diamicron® MR 60 mg tablets.

For Test A2 *versus* Reference comparison, the Test A2-to-Reference GMR and corresponding 90% CI are within the acceptance range of 80.00% to 125.00%, for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.
For Test B2 *versus* Reference comparison, the pharmacokinetic results show that the Test-to-Reference GMR for C_{max} and the lower limit of the 90% CI interval is below the lower limit of the acceptance range.

	For AUC_{0-t} and $AUC_{0-\infty}$, the Test-to-Reference GMR and 90% CI interval are all within the bioequivalence acceptance range of 80.00% to 125.00%.
Safety Results:	*Group 1* Overall, 24 subjects received at least one of the investigational products. There was no relevant difference between Test A1, Test A2, Test A3, and Reference product regarding the frequency of treatment-emergent AEs (TEAEs). However, the frequency of drug-related TEAEs was lower in Test A3 compared to the Reference product (5 subjects, 22% *versus* 10 subjects, 42%). In total, the most common treatment-emergent AEs (TEAEs) were hypoglycemia and headache, reported by 16 (67%) and 8 (33%), respectively. Among the 41 hypoglycemia episodes (reported in 16/24 subjects, 67%), all were asymptomatic except for 4 episodes in 3 subjects, 1 was moderate in intensity; all were considered drug-related and were recovered after dextrose solution administration. The majority of the TEAEs experienced on Group 1 were deemed mild in intensity (78/93 TEAEs, 84%). Some were moderate (15/93 TEAEs, 16%) and none was severe. One (1) TEAE was recovering by the end of study and the others were considered recovered/resolved. There were no serious AEs (SAEs), nor discontinuations due to TEAEs. *Group 2* Overall, 24 subjects received at least one of the investigational products. There was no relevant difference between Test B1, Test B2, and Reference product regarding the frequency of TEAEs. However, for Test B3, the number of subjects having at least one TEAE was lower compared to the Reference product (8 subjects, 33% *versus* 14 subjects, 58%). The frequency of drug-related TEAEs was also lower for Test B3 compared to the Reference product (4 subjects, 17% *versus* 14 subjects, 58%). In total, the most common TEAEs were hypoglycemia and headache, reported by 22 (92%) and 9 (38%), respectively. Among the 66 hypoglycemia episodes (reported in 22/24 subjects, 92%), all were asymptomatic except one episode, 1 was moderate in intensity; all were considered drug-related and were recovered after dextrose solution administration. The majority of the TEAEs experienced on Group 2 were deemed mild in intensity (96/114 TEAEs, 84%). Some were moderate (18/114 TEAEs, 16%) and none was severe. Three (3) TEAEs were recovering by the end of study and the

	others were considered recovered/resolved. There were no SAEs, nor discontinuations due to TEAEs. *Group 3* Overall, 20 subjects received at least one of the investigational products. There was no relevant difference between Test A2 and Reference product regarding the frequency of TEAEs. However, for Test B2, the number of subjects having at least one TEAE was lower compared to the Reference product (10 subjects, 50% *versus* 15 subjects, 75%). The frequency of drug-related TEAEs was also lower for Test B2 compared to the Reference product (8 subjects, 40% *versus* 14 subjects, 70%). In total, the most common TEAEs were hypoglycemia and headache, reported by 17 (85%) and 4 (20%), respectively. Among the 41 hypoglycemia episodes (reported in 17/24 subjects, 85%), all were asymptomatic except for 5 episodes reported by 3 subjects, 1 was moderate in intensity; all were considered drug-related and were recovered after dextrose solution administration. The majority of the TEAEs experienced on Group 3 were deemed mild in intensity (52/55 TEAEs, 95%). Some were moderate (3/55 TEAEs, 5%) and none was severe. Two (2) TEAEs were recovering by the end of study and the others were considered recovered/resolved. There were no SAEs, nor discontinuations due to TEAEs.
Conclusion:	This study was a single-center, single-dose, open-label, laboratory-blinded, randomized: – Group 1 and Group 2: five-treatment, three-sequence, five-period crossover exploratory study under fasting conditions. – Group 3: three-treatment, two-sequence, three-period crossover exploratory study under fed conditions. In comparison to two Diamicron® MR 60 mg tablets (Reference product; from Les Laboratoires Servier), Gliclazide MR 120 mg tablets formulation (Test A) with fast release rate (Test A1) showed a similar bioavailability on the rate (as assessed by C_{max}) and extent (as assessed by AUC_{0-t} and $AUC_{0-\infty}$) of gliclazide absorption, under fasting conditions. Gliclazide MR 120 mg tablets formulation (Test A) with the medium release rate (Test A2) and slow release rate (Test A3) showed similar bioavailability in comparison to two Diamicron® MR 60 mg tablets (Reference product; from Les Laboratoires Servier) on the extent (AUC_{0-t} and $AUC_{0-\infty}$) of gliclazide absorption, but showed a lower bioavailability on the rate (C_{max}) of gliclazide absorption, under fasting conditions. In comparison to two Diamicron® MR 60 mg tablets (Reference product; from Les Laboratoires Servier), Gliclazide MR 120 mg

	tablets formulation (Test B) with fast release rate (Test B1) showed a similar bioavailability on the rate (C_{max}) and extent (AUC_{0-t} and $AUC_{0-\infty}$) of gliclazide absorption, under fasting conditions. Gliclazide MR 120 mg tablets formulation (Test B) with the medium release rate (Test B2) and slow release rate (Test B3) showed similar bioavailability in comparison to the two Diamicron® MR 60 mg tablets (Reference product; from Les Laboratoires Servier) on the extent (AUC_{0-t} and $AUC_{0-\infty}$) of gliclazide absorption, but showed lower bioavailability on the rate (C_{max}) of gliclazide absorption, under fasting conditions. In comparison to the two Diamicron® MR 60 mg tablets (Reference product; from Les Laboratoires Servier), the Gliclazide MR 120 mg tablets formulation (Test A) with medium release rate (Test A2) showed similar bioavailability on the rate (C_{max}) and extent (AUC_{0-t} and $AUC_{0-\infty}$) of gliclazide absorption, under fed conditions. However, the Gliclazide MR 120 mg tablets formulation (Test B) with medium release rate (Test B2) showed similar bioavailability in comparison to the two Diamicron® MR 60 mg tablets (Reference product; from Les Laboratoires Servier) on the rate (C_{max}), but showed lower bioavailability on the rate (C_{max}) of gliclazide absorption, under fed conditions. The two Gliclazide MR 120 mg tablets formulations Test A and Test B with slow, medium and fast release rate and the two Diamicron® MR 60 mg tablets were well tolerated after single administration in fasting and fed conditions. There were no safety concerns during the study.
Date of Report:	21JUN2024