These Clinical Trial Results are provided for informational purposes only.

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2. SYNOPSIS

Name of Sponsor: Name of Finished Product: N/A Name of Active Ingredient: CS-917	Individual Trial Table Referring to Part 9.5.1 of the Dossier Volume: Page:	(For National Authority Use only)

Title of Trial: The effect of the co-administration of multiple oral doses of the fructose-1,6-bisphosphatase (FBPase) inhibitor CS-917 and glibenclamide on pharmacokinetics, safety and tolerability in diabetic patients (NIDDM)

Protocol no.: CS0917-A-E107

EudraCT no.: 2004-003195-11

Investigators:

[redacted]

Trial Centre:

PAREXEL International GmbH
Clinical Pharmacology Research Unit
Klinikum Westend, Haus 18
Spandauer Damm 130
D–14050 Berlin, Germany

Publication (reference):

None at the time of this report

Trial Period:	Phase of Development:
Initiation date: 26 Jan 2005 Completion date: 11 May 2005	Phase I

Trial Objectives:

The primary objective was to assess the effects of CS-917 on the plasma PK of glibenclamide and the effects of glibenclamide on the plasma PK of CS-917, the intermediate metabolite R-134450, the active metabolite R-125338 and the metabolite R-143047 at steady-state in NIDDM patients.

The secondary objective was to assess the safety and tolerability of CS-917 alone, of glibenclamide alone and of CS-917 in combination with glibenclamide in NIDDM patients and to assess the effect of co-administration of CS-917 and glibenclamide on plasma glucose and lactic acid concentrations.

Trial Hypothesis:

The PK of CS-917 is not influenced by co-administration with glibenclamide and glibenclamide PK is not influenced by co-administration with CS-917.

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Methodology:

This was a Phase I, randomised, open-label, three-way crossover, single-centre study with three treatment periods of 14 days each, separated by washout periods of at least 14 days, each. A total of 19 male and 2 female subjects with type 2 diabetes mellitus (NIDDM) were enrolled. After a 14-day washout period for subjects receiving oral anti-diabetics, subjects were administered multiple doses of 200 mg CS-917 as 2x50 mg tablets twice daily (*b.i.d.*) from Day 1 to Day 5 and of 200 mg *b.i.d.* CS-917 as 200 mg tablets from Day 6 to Day 13, plus 200 mg in the morning of Day 14 (Treatment A), multiple doses of 3.5 mg glibenclamide tablet once daily (*o.d.*) for an additional 14 days (Treatment B) and a 14-day co-administration of multiple doses of CS-917 and glibenclamide (Treatment C). Subjects were titrated from 100 mg *b.i.d.* CS-917 to 200 mg *b.i.d.* CS-917, if morning fasting glucose levels did not fall below 5.6 mmol/L (100 mg/dL) and lactic acid values were below 4.5 mmol/L.

Subjects were admitted to the Clinical Pharmacology Research Unit (CPRU) in the morning of Day –1, at least 24 hours before the first dosing and remained at the CPRU until Day 15. Dosing was performed after an overnight fast in the morning and in the evening on Days 1 to 13 and on Day 14 in the morning only.

Safety evaluation of subjects included physical examination, vital signs, 12-lead ECG (electrocardiogram), AEs, laboratory parameters (biochemistry, haematology, urinalysis), plasma glucose, and lactic acid.

A final examination was performed 7 to 14 days after the last PK sample of the last treatment period. The total duration of the study for a single subject completing all three treatment periods was approximately 115 days, not including the time span between screening and Day –1 and a possible safety follow-up.

Duration of Treatment:

CS-917 and glibenclamide were administered over 14 days.

CS-917
100 mg *b.i.d.*, administered as 2 x 50-mg tablets *b.i.d.*, from Day 1 to Day 5; total daily dose 200 mg, followed by
200 mg *b.i.d.*, administered as 1 x 200-mg tablets *b.i.d.*, from Day 6 to Day 14, total daily dose 400 mg; Day 14 morning dose only.

Glibenclamide
3.5 mg, administered as a 3.5 mg tablet *o.d.* in the morning on Day 1 to Day 14.

Number of Subjects: 21 subjects with type 2 diabetes mellitus (NIDDM)

Screened: 76

Planned: 24

Enrolled/Randomised: 21

Completed: 20

Discontinued: 1

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Diagnosis and Main Criteria for Inclusion:

The participants of this trial were 21 male or female subjects with type 2 diabetes mellitus (NIDDM); diet-treated or where it was medically justifiable to withdraw oral anti-diabetic treatment during the study; negative serum pregnancy test at screening and check-in of each period in females; 18 to 70 years of age (inclusive); BMI 22–35 kg/m^2; HbA_{1C} of ≥6.5% and <10% at screening; fasting plasma glucose ≤11.1 mmol/L (<200 mg/dL) and during the washout phase and on Day –1 prior to first dosing: 8.9–13.9 mmol/L (160–250 mg/dL), inclusive; if the fasting blood glucose was >11.1 mmol/L on one occasion, the assessment was repeated and the subject could be included as judged by the Investigator. Subjects were normotensive or had stable blood pressure on antihypertensive medication; negative drug and alcohol screening; no laboratory value outside the normal laboratory reference range at screening and before randomisation, no clinically relevant abnormality in the electrocardiographic examinations (ECG), negative results in human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) tests. All subjects freely gave informed consent in writing.

Investigational Product and Comparator Information:

Dosage Form: 50 mg and 200 mg tablets CS-917

Route of Administration: Oral

Lot No.: [redacted] and [redacted]

Expiry Date: 07/2005

Dosage Form: 3.5 mg tablets glibenclamide (Euglucon N®)

Route of Administration: Oral

Lot No.: [redacted]

Expiry Date: 07/2005

Pharmaceutical Manufacturer: Aventis Pharma Deutschland GmbH

Criteria for Evaluation:

Pharmacokinetics / Pharmacodynamics:

The following pharmacokinetic parameters were calculated using a non-compartmental approach: $AUC_{SS,0-\tau}$, $C_{SS,max}$, $C_{SS,min}$, t_{max}, $t_{1/2}$, V_{SS}/f, $MRT_{SS,0-\infty}$, CL_{SS}/f (the latter three parameter for CS-917 and glibenclamide only).

For pharmacodynamic evaluation, AUC_{0-6} and AUC_{0-24} for plasma glucose and plasma lactic acid were derived from the blood levels and compared between the treatments.

Efficacy:

Not applicable.

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Safety:

Physical examination, vital signs, 12-lead ECG (electrocardiogram), adverse events, laboratory parameters (biochemistry, haematology, urinalysis), blood glucose, and lactic acid.

Statistical Methods:

All quantitative data were presented by treatment, sequence, and time point using descriptive statistics: Arithmetic mean, standard deviation, median, number of observations as well as minimum and maximum values. For log-normally distributed pharmacokinetic parameters, geometric CV was also determined. For categorical data, frequency tables were given. Profiles of time-dependent variables as well as the respective means and medians were presented graphically.

The statistical comparisons were of the equivalence type whereby the two one-sided tests approach at the 5% level was used in conjunction with an analysis of variance model appropriate for the cross-over design using log-transformed values for the evaluation of $AUC_{SS,0-\tau}$ and $C_{SS,max}$. The geometric mean ratios of $AUC_{SS,0-\tau}$ and $C_{SS,max}$ had to lay within 80–125% with 90% confidence. Corresponding non-parametric methods (Hodges-Lehmann intervals) were applied to untransformed t_{max} estimates. The treatment regimes were compared as follows (test *vs.* reference):

CS-917 + glibenclamide *vs*. CS-917 and CS-917 + glibenclamide *vs*. glibenclamide.

AUC_{0-6} and AUC_{0-24}, as well as maximum absolute changes and percent changes of plasma glucose and plasma lactic acid concentrations within 6 hours after the morning dosing were tabulated per time point by treatment on Day 14. Measured values of fasting glucose and lactic acid were compared between treatments by means of descriptive statistics.

Summary statistics were tabulated to assess safety and tolerability terms of adverse events, laboratory tests, 12-lead ECG, blood pressure, pulse rate, and physical examinations.

Summary:

Pharmacokinetic/Pharmacodynamic Results:

For glibenclamide, bioequivalence to co-administration of CS-917 with glibenclamide was established. All respective point estimates and the corresponding 90% CIs for the primary PK parameters $AUC_{SS,0-\tau}$ and $C_{SS,max}$ were within the limits of bioequivalence [0.8, 1.25] with one exception: the upper bound of the 90% CI of glibenclamide $C_{SS,max}$ (1.389) fell outside the bioequivalence limit. Also, the corresponding point estimate indicated an increase in $C_{SS,max}$ by 14.8% when glibenclamide was co-administered with CS-917 compared with glibenclamide given alone. Although statistically significant, this modest increase in glibenclamide $C_{SS,max}$ was not considered to be clinically significant.

Vice versa, co-administration of repeated doses of CS-917 with glibenclamide did not influence plasma pharmacokinetics of CS-917 or any of its metabolites to a statistically significant or clinically relevant degree. All point estimates test *vs.* reference and the corresponding 90% CIs for the primary PK parameters $AUC_{SS,0-\tau}$ and $C_{SS,max}$ were within the limits of the bioequivalence criteria [0.8, 1.25].

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Synopsis Table 1: Summary Table of Pharmacokinetic Parameters of Glibenclamide, CS-917, R-125338, R-134450 and R-143047 in Plasma by Treatment After Repeated Doses (Day 14)

Analyte	Parameter	Statistics	Treatment A N = 21	Treatment B N = 21	Treatment C N = 20
Gliben-clamide	$AUC_{SS,0-\tau}$ [ng•h/mL]	G mean	–	627.4 (17.15)	666.4 (14.15)
	$C_{SS,max}$ [ng/mL]	G mean	–	174.019 (20.36)	207.694 (18.82)
CS-917	$AUC_{SS,0-\tau}$ [ng•h/mL]	G mean	1988.2 (25.88)	–	1987.4 (29.19)
	$C_{SS,max}$ [ng/mL]	G mean	1799.967 (25.34)	–	1814.754 (28.89)
	$t_{SS,max}$ [h]	Median	0.7 (0.3–1.5)	–	0.7 (0.3–0.7)
	$t_{SS,1/2}$ [h]	A mean	0.67 (0.38)	–	0.71 (0.43)
R-125338	$AUC_{SS,0-\tau}$ [ng•h/mL]	G mean	5822.3 (19.31)	–	5708.5 (22.46)
	$C_{SS,max}$ [ng/mL]	G mean	1069.127 (18.44)	–	1043.249 (23.83)
	$t_{SS,max}$ [h]	Median	2 (1–2.5)	–	2 (1.5–3)
	$t_{SS,1/2}$ [h]	A mean	77.23 (19.96)	–	82.75 (21.49)
R-134450	$AUC_{SS,0-\tau}$ [ng•h/mL]	G mean	1182.6 (21.14)	–	1167.8 (26.83)
	$C_{SS,max}$ [ng/mL]	G mean	365.859 (24.06)	–	364.233 (31.46)
	$t_{SS,max}$ [h]	Median	1 (0.7–2)	–	1 (0.7–2)
	$t_{SS,1/2}$ [h]	A mean	2.04 (0.4)	–	3.51 (6.44)
R-143047	$AUC_{SS,0-\tau}$ [ng•h/mL]	G mean	15151.5 (23.17)	–	15470.4 (21.70)
	$C_{SS,max}$ [ng/mL]	G mean	1423.465 (22.26)	–	1460.774 (21.46)
	$t_{SS,max}$ [h]	Median	3 (0–12)	–	3.5 (0.3–6)
	$t_{SS,1/2}$ [h]	A mean	35.99(5.43)	–	35.59 (5.15)

Treatment A: 100 mg *b.i.d.* CS-917 (5 days) followed by 200 mg *b.i.d.* CS-917 (8 days) plus 200 mg in the morning of Day 14;
Treatment B: 3.5 mg *o.d.* glibenclamide (14 days);
Treatment C: A + B;
G mean = geometric mean (CV_b%); Median (min–max); A mean = arithmetic mean (SD)

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Synopsis Table 2: Point Estimates and 90% CIs for the Ratios of the Treatments

Analyte	Parameter	Treat-ment Ratio	Estimate	Lower Bound of CI	Upper Bound of CI
Gliben-clamide	$AUC_{SS,0-\tau}$ [ng•h/mL]	C *vs.* B	1.036	0.912	1.176
	$C_{SS,max}$ [ng/mL]	C *vs.* B	1.148	0.949	**1.389**
	$t_{SS,max}$ [h]	C *vs.* B	0.000	–0.500	0.000
CS-917	$AUC_{SS,0-\tau}$ [ng•h/mL]	C *vs.* A	1.040	0.948	1.142
	$C_{SS,max}$ [ng/mL]	C *vs.* A	1.052	0.975	1.135
	$t_{SS,max}$ [h]	C *vs.* A	0.000	0.000	0.000
R-125338	$AUC_{SS,0-\tau}$ [ng•h/mL]	C *vs.* A	0.996	0.904	1.098
	$C_{SS,max}$ [ng/mL]	C *vs.* A	0.992	0.878	1.122
	$t_{SS,max}$ [h]	C *vs.* A	0.000	–0.500	0.500
R-134450	$AUC_{SS,0-\tau}$ [ng•h/mL]	C *vs.* A	1.019	0.881	1.180
	$C_{SS,max}$ [ng/mL]	C *vs.* A	1.040	0.895	1.208
	$t_{SS,max}$ [h]	C *vs.* A	0.000	–0.340	0.000
R-143047	$AUC_{SS,0-\tau}$ [ng•h/mL]	C *vs.* A	1.028	0.954	1.108
	$C_{SS,max}$ [ng/mL]	C *vs.* A	1.034	0.955	1.119
	$t_{SS,max}$ [h]	C *vs.* A	0.660	–0.500	1.840

Treatment A: 100 mg *b.i.d.* CS-917 (5 days) followed by 200 mg *b.i.d.* CS-917 (8 days) plus 200 mg in the morning of Day 14;
Treatment B: 3.5 mg *o.d.* glibenclamide (14 days);
Treatment C: A + B; Parameters outside the bioequivalency limits [0.80, 1.25] are marked in **bold**

On Day 14, both monotherapies and the combination therapy lowered post-prandial plasma glucose values within 6 hours post-dose (AUC_{0-6}) and over a 24-h period (AUC_{0-24}) (see Synopsis Figure 1 and Synopsis Table 3). The plasma glucose lowering effect was most pronounced for glibenclamide monotherapy and for glibenclamide in combination with CS-917. These two treatment regimens showed similar decreases for AUC_{0-6} by 20% and a slight additive effect of the combination therapy on AUC_{0-24} by about 25% (probably as a result of the additional evening dose of CS-917 in the combination regimen).

On Day 14, the post-dose plasma lactic acid AUC_{0-6} values were increased approximately by 50% after CS-917 (either alone or in combination with glibenclamide) compared with glibenclamide alone. Over 24 hours, this effect of CS-917 on plasma lactic acid was alleviated and AUC_{0-24} values were comparable between the three treatments (see Synopsis Figure 2 and Synopsis Table 3).

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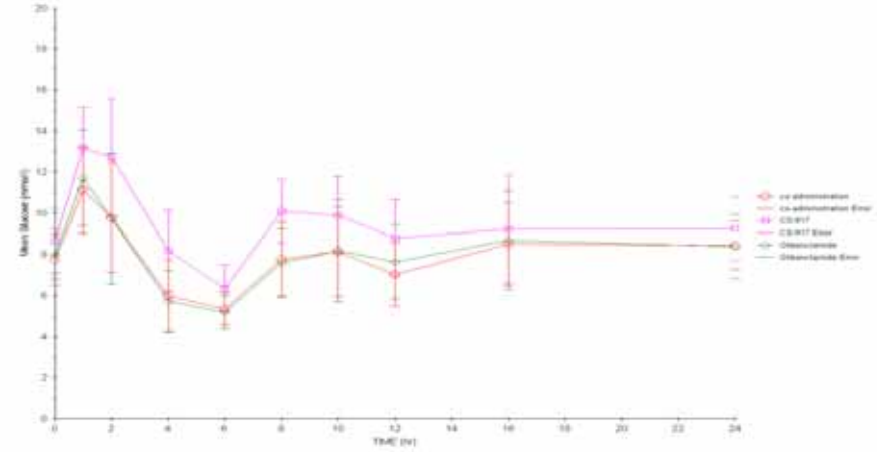
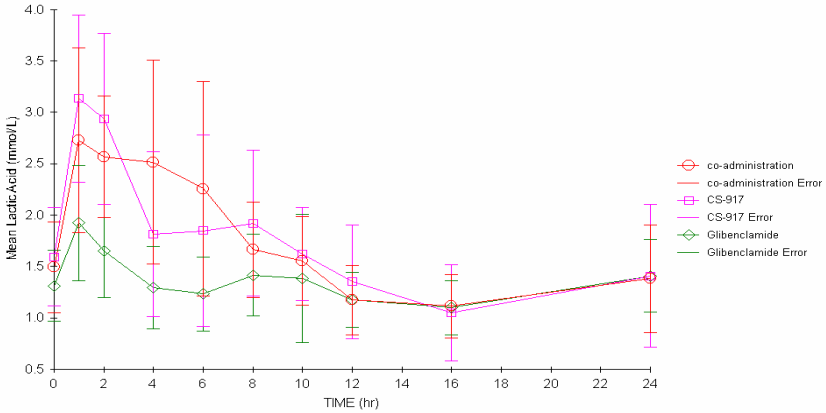


Synopsis Figure 1: Mean ±SD Post-dose Plasma Glucose Concentration on Day 14



Synopsis Figure 2: Mean ±SD Post-dose Plasma Lactic Acid Concentration on Day 14

Synopsis Table 3: Plasma Glucose or Lactic Acid AUC_{0-6} and AUC_{0-24} [mmol•h/L] by Treatment (Day 14)

	Parameter	Statistics	Treatment A (N = 21)	Treatment B (N = 21)	Treatment C (N = 20)
Glucose	**AUC_{0-6} [mmol•h/L]**	A Mean	59.5 (±10.4)	47.0 (±9.3)	47.0 (±7.9)
	AUC_{0-24} [mmol•h/L]	A Mean	180.7 (±45.2)	144.8 (±51.1).	137.1 (±39.2)
Lactic acid	**AUC_{0-6} [mmol•h/L]**	A Mean	13.9 (±4.1)	8.9 (±1.9)	14.6 (±2.7)
	AUC_{0-24} [mmol•h/L]	A Mean	38.8 (±9.4)	31.4 (±5.9)	39.0 (±7.2)

Treatment A: 100 mg *b.i.d.* CS-917 (5 days) followed by 200 mg *b.i.d.* CS-917 (8 days) plus 200 mg in the morning of Day 14; Treatment B: 3.5 mg *o.d.* glibenclamide (14 days); Treatment C: A + B
A Mean = Arithmetic mean (±SD)

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Safety Results:

Overall, glibenclamide and CS-917 were well tolerated and safe when given alone. Although co-administration of multiple doses of CS-917 and glibenclamide did not result in an increased incidence of AEs and had no impact upon the frequency of AEs with combination therapy compared to the respective single administrations, caution should be taken. For about 40% of the subjects on the combination therapy in this study, administration of CS-917 + glibenclamide needed to be reduced on occasional days.

No deaths, serious AEs, or other significant AEs occurred during this study. There were 33 AEs reported from 11 subjects (52.4%). The majority of AEs (n = 23) in 8 subjects (38.1%) were considered possibly related to the study drug. All AEs were mild to moderate in severity. The gastrointestinal system was most frequently affected (6 subjects), followed by the nervous system (4 subjects).

In 3 subjects, a total of 6 hypoglycaemic AEs (<45 mg/dL or <2.5 mmol/L) requiring remedial oral glucose occurred. During treatment with glibenclamide alone, 2 subjects had 5 hypogylcaemic AEs. During co-administration of glibenclamide and CS-917, 1 subject had 1 hypoglycaemic AE. There were no AEs of hypoglycaemia in subjects treated with CS-917 monotherapy. None of these hypoglycaemic AEs resulted in withdrawal from the study.

Daily pre-dose fasting plasma lactic acid values were transiently elevated (>4.5 mmol/L) in two individuals while on glibenclamide monotherapy. No clinically overt symptoms of lactic acidosis occurred in any subject. There were no consistent drug-related elevations in daily pre-dose fasting plasma lactic acid levels in any subject during the study course. There was no general trend towards elevated bicarbonate levels for any treatment administered.

Apart from this, no clinically significant changes or differences between treatments were reported for safety laboratory (haematology, clinical chemistry and urinalysis), supine vital signs (systolic and diastolic blood pressure, and pulse rate), 12-lead ECG, and physical examination.

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Conclusions:

- Co-administration of repeated doses of glibenclamide with CS-917 did not influence the plasma pharmacokinetics of CS-917 or any of its metabolites to a statistically significant or clinically relevant degree.
- In case of glibenclamide, concomitant administration of the multiple doses of CS-917 did not significantly affect the total exposure ($AUC_{SS,0-\tau}$) of glibenclamide itself. However, the peak exposure ($C_{SS,max}$) of glibenclamide was 14.8% higher when administered with CS-917 than when it was administered alone. This observed difference was statistically significant but not considered clinically significant.
- Overall, multiple doses of CS-917 and glibenclamide administered over 14 days were safe and well tolerated when given as monotherapies in NIDDM patients in this study. In terms of combination therapy a potential decrease of blood glucose should be taken into account.
- Hypoglycaemic AEs, which required remedial oral glucose therapy, occurred exclusively during glibenclamide monotherapy (2 subjects with 5 AEs) or during combination with CS-917 (1 subject with 1 AE).
- Two subjects each showed a single potentially critical transient elevation of lactic acid concentrations >4.5 mmol/L during treatment with glibenclamide monotherapy. There were no clinically overt symptoms in any subject. There appeared to be no effect upon daily pre-dose fasting lactic acid values after any of the three treatments over the course of the study.

Date of the Report: 05-July-2006