Document title	**Clinical Study Report Synopsis**
Study title	**Dose ranging study of S44497 administered orally once daily for four weeks in type 2 diabetic patients. A multicentre, randomised, double-blind, double-dummy, phase II study versus placebo and glimepiride and sitaglipin.**
Study drug	**S 44497**
Studied indication	**Type 2 Diabetes**
Development phase	**Phase II**
Protocol code	**CL2-44497-004**
Study initiation date	**19 February 2008**
Study completion date	**28 April 2009**
Main coordinator	[redacted] **Germany**
Sponsors	**Institut de Recherches Internationales Servier (I.R.I.S.) 50 Rue Carnot, 92284 Suresnes Cedex - France** **Laboratorios Servier, Avenida de los Madronos 33, 28043 Madrid - Spain** **Servier Research and Development Ltd., International Centre for Therapeutic Research, Wexham Springs, Framewood Road, Wexham, Slough SL3 6RJ - UK** **Servier Canada Inc., 235 Armand-Frappier Blvd., Laval, Quebec - Canada**
Responsible medical officer	[redacted]
GCP	**This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.**
Date of the report	**Final version of 22 July 2010**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: **I.R.I.S.** **6 place des Pleiades** **92415 Courbevoie - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
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Title of study:

Dose ranging study of S 44497 administered orally once daily for four weeks in type 2 diabetic patients.
A multicentre, randomised, double-blind, double-dummy, phase II study *versus* placebo and glimepiride and sitagliptin.
Protocol No.: CL2-44497-004
EudraCT number: 2007-003808-35

International Coordinator: [redacted] Germany

Study centres:

9 centres amended to 12 centres (Amendments Nos. 2, 4), then increased to 13 centres to reach the target number of patients, in 5 countries (4 initially planned and 1 added by Amendment No. 2) included at least one patient: Canada (1 centre - 18 patients), Germany (4 centres – 84 patients), Russian Federation (6 centres, 57 patients), Spain (1 centre - 8 patients), and United Kingdom (UK) (1 centre – 1 patient).

Publication: Not applicable

Studied period:	**Phase of development of the study:**
Initiation date: 19 February 2008 (first patient screened) Completion date: 28 April 2009 (date of last patient completed visit)	Phase II

Objectives:

The purpose of this exploratory clinical research was to assess the efficacy of S 44497, based on the glucose profile in type 2 diabetic patients in order to determine the range of doses to be evaluated in the next stage of development. The efficacy and safety of S 44497 administered over 4 weeks was compared with a placebo, another DPP-4 inhibitor (sitagliptin) and an established sulfonylurea (glimepiride). The pharmacokinetic and pharmacodynamic profiles of S 44497 were also assessed.

Primary objective

- To evaluate the dose-effect relationship of S 44497 and its efficacy by comparison with placebo group, using the 24-hour profile of plasma glucose.

Secondary objectives

- To evaluate the pharmacodynamic profile of S 44497 based on insulin, C-peptide, GLP-1, glucagon and DPP-4 activity levels.
- To evaluate the efficacy of S 44497 based on fasting plasma glucose and HbA1c.
- To assess the pharmacokinetics of S 44497 and metabolites, if applicable, after a single and repeated administration at doses of 50, 100, 150, 200 and 300 mg.
- To perform an exploratory comparison *versus* glimepiride and sitagliptin.
- To assess the safety profile of S 44497 (adverse events, hypoglycaemic episodes, biochemistry and haematology, ECG, vital signs and body weight).

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Methodology:

A prospective, multinational, multicentre, randomised, comparative, double-blind, double-dummy, placebo controlled, parallel dose ranging study, consisting of:

- A 3-week run-in period placebo for treatment naïve patients or placebo/wash-out for patients previously on oral hypoglycaemic agent, or according to Amendment No. 2 a 4-week run-in period for patients previously on metformin (and 3-week for other patients).
- A 4-week double-blind treatment period with S 44497 (at 5 different doses), placebo, glimepiride or sitagliptin (*i.e.* 8 parallel groups).
- A 1-week follow-up visit (Amendment No. 1) with a visit to be scheduled 3 to 7 days after the last study drug administration.

Patients were hospitalised from D-1 evening (the evening preceding inclusion; D0) to D2 after lunch and from D27 evening to D29 morning for the pharmacokinetic and pharmacodynamic blood and urine sampling. Patients received similar standardised meals at D0, D1 and D28.

Number of patients:

Planned inclusion: 160 patients (20 per group).

Included: 168 patients and 164 patients in the Included Set (4 patients were included and completed the study twice but these 2nd inclusions were not taken into account in the statistical analyses).

Diagnosis and main criteria for inclusion:

Type 2 diabetic outpatients diagnosed for more than 3 months according to WHO criteria, male or female (non-childbearing potential; either surgically sterilised or post-menopausal), aged between 35 and 65 years old, body mass index (BMI) 24-38 kg/m^2 inclusive. Patients were to be currently treated with diet alone or on monotherapy with a stable dose of an oral sulfonylurea, glinide or α-glucosidase inhibitor, or metformin (added by Amendment No. 2) prescribed for at least three months. Patients should have been suboptimally controlled with values of HbA1c (measured at selection) between 7.0 and 9.5% inclusive, (modified by Amendment No. 4, as HbA1c between 6.8 and 9.5% inclusive for patients on diet alone, and between 6.5 and 9.5% inclusive for patients on oral antidiabetic drug (OAD) treatment), C-peptide ≥ 0.5 nmol/L (sampled at screening visit and assessed at selection visit), and fasting plasma glucose > 7.8 mmol/L (140 mg/dL) and < 13.8 mmol/L (250 mg/dL) (measured at selection and inclusion).

Study drug: S 44497 (five doses: 50 mg, 100 mg, 150 mg, 200 mg and 300 mg) were administered orally once daily in the morning just before breakfast.

Batch Nos. L0020407, L0020409, L0023491, L0026071

Reference products:

The comparators were administered once daily in the morning just before breakfast:

- Placebo capsules.
- Sitagliptin (Januvia™) 100 mg encapsulated tablets.
- Glimepiride (Amaryl™) 2 mg or 4 mg encapsulated tablets. The 2 mg dose was administered for the first week and then adjusted according to safety criteria to 4 mg (or left at 2 mg) for the following 3 weeks until the end of the study.

Duration of treatment:

- A 3 to 4-week placebo wash-out/run-in period.
- A 4-week active treatment period.
- A 1-week follow-up period without study treatment.

During the run-in period and the treatment period, in order to maintain the blind, patients received 7 capsules administered once daily:

- 6 capsules of identical appearance (mid size, size 0) containing either S 44497 (one of the 5 dosages), glimepiride or placebo.
- 1 capsule of identical appearance (big size, Dbcap size AAA) containing either sitagliptin or placebo.

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Criteria for evaluation:

Efficacy measurements

- Plasma glucose profile at D0 (before drug administration) and D28 at the same time points: sampling at T-15 min before drug administration and at minutes: 30 (T0.5), 60 (T1), 120 (T2), 180 (T3), 240 (T4), 300 (T5), 360 (T6), 420 (T7), 660 (T11), 720 (T12), 780 (T13), 840 (T14) and T24 (hours).
- Fasting plasma glucose (FPG) on D0, D1, D2, D7, D14, D21, D28 and D29 (T-15 min).
- Glycated Haemoglobin (HbA1c) at the selection and at the end of the study drug treatment period (D29).
- Insulin profile on D0 and D28 (T-15 min, 30, 60,120, 180, 240, 660, 720, 780, 840 min and 24 h).
- C-peptide and Glucagon-like peptide-1 (GLP-1) profiles on D0 and D28 (T-15 min, 60, 120, 180, 240, 660, 720, 780, 840 min and 24 h).
- Glucagon: four-hour profile on D0 and D28, and according to Amendment No. 4: T-15 min, 30, 60, 120, 180, 240 min on D0 and D28.
- DPP-4 activity profile on D1 and D28 (T-15 min, 30, 60, 120, 180, 240, 360, 660, 840 min, and 24 h).

Safety measurements

- Adverse events and hypoglycaemia episodes assessed at all visits.
- Biochemistry [sodium, potassium, chloride, calcium, total protein, albumin, urea, creatinine, CPK, alkaline phosphatase, Aspartate aminotransferase (ASAT), ALanine aminotransferase (ALAT), Gamma-glutamyl transferase (GGT), total bilirubin] and haematology [red blood cells, haemoglobin, haematocrit, Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC), white blood cells, lymphocytes, monocytes, eosinophils, basophils, neutrophils, platelets] at screening, selection, D0, D2, D14, and D29.
  Triglycerides on D0 (T –15, 120, 180, 240 and 660 min) and D28 (T –15, 120, 180, 240, 360 and 660 min)
- Physical examination at screening, inclusion, D14 and D29.
- Vital signs (blood pressure and heart rate) at all visits.
- Weight measured at screening, inclusion, D–1, D0, D14, and D27/28.
- ECG on D0, D1, D14, and D27/28.

Pharmacokinetic measurements

Blood samples (on D1, D2, D7, D14, D21, D28 and D29) and urine samples (on D1 and D28) were collected in order to assess S 44497 (and its metabolites). The analysis was performed using validated procedures and methods. Pharmacokinetics results are presented fully in the reports in Appendix 16.3.

Statistical methods:

The Randomised Set (RS) was defined as all included patients to whom a therapeutic unit was randomly assigned.

Efficacy analyses: were carried out primarily on the Full Analysis Set (FAS) and secondarily on the Per Protocol Set (PPS). The FAS based on the intention-to-treat principle, defined as all randomised patients who have taken at least one dose of study treatment and who have at least one baseline (D0) and one post-baseline evaluation of the plasma glucose profile. The PPS was defined as patients of the FAS without any relevant protocol deviation which could affect the evaluation of the plasma glucose profile (at baseline or at D28). More precisely, the glucose level had to be assessed just before each meal, 1 hour and 2 hours after each meal, and in an acceptable period of time around the theoretical time.

- Primary criterion: Plasma glucose profile based on a 24-hour Area Under the Curve (AUC) at D0 and D28, expressed as mean change in $AUC_{0\text{-}24h}$ and mean change in weighted AUC ($WAUC_{0\text{-}24h}$).

Main analysis: comparison of the treatment effect for each dose of S 44497 *versus* placebo group on the change from baseline to last post-baseline value, studied using an analysis of covariance (general linear model) with baseline and centre (fixed effects) as covariates. The estimate of the treatment difference, its standard error, its 2-sided 95% confidence interval were provided.

Secondary analyses: descriptive statistics were provided by group for the value at each visit and for the change from D0 value to D28 value. A comparison between each comparator (glimepiride and sitagliptin) and each dose of S 44497 on the one hand and placebo on the other were provided with the same methodology as the main analysis.

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Statistical methods (Cont'd):

- Secondary criteria

Descriptive statistics on all analytical approaches of each criterion were provided by group. Graphs were provided by group for the change from baseline value to the last post-baseline value of each criterion.

Safety analysis

Descriptive statistics were provided on the Safety Set for safety parameters.

SUMMARY - CONCLUSIONS

STUDY POPULATION AND OUTCOME

Overall, 236 patients were selected for the study of which 164 were included and randomly assigned to a treatment group (Tables 1 and 2). The distribution between the 8 groups was well balanced with 19 to 23 patients/group. During the study, 9 patients (5.5%) were prematurely withdrawn, all due to lack of efficacy, and 155 patients (94.5%) completed the study.

Table 1 - Disposition of patients in the S 44497 groups

		S 44497				
		50 mg	**100 mg**	**150 mg**	**200 mg**	**300 mg**
Included (randomised)	**n**	**21**	**19**	**20**	**23**	**19**
Lost to Follow-up	**n**	-	-	-	-	-
Withdrawn						
due to lack of efficacy	n	2	-	-	2	1
Completed	**n**	**19**	**19**	**20**	**21**	**18**
Full Analysis Set (FAS)	n (%)	19 (90.5)	19 (100)	20 (100)	21 (91.3)	18 (94.7)
Per Protocol Set (PPS)	n (%)	16 (76.2)	18 (94.7)	15 (75.0)	17 (73.9)	16 (84.2)
Safety set	n (%)	21 (100)	19 (100)	20 (100)	23 (100)	19 (100)

n number of assessable patients; Percentage calculated as percentage of the randomised patients

Table 2 - Disposition of patients in the S 44497 pooled group and comparator groups

		All S 44497	**Placebo**	**Sitagliptin**	**Glimepiride**	**All**
Included (randomised)	**n**	**102**	**23**	**20**	**19**	**164 (100)**
Lost to Follow-up	**n**	-	-	-	-	-
Withdrawn						
due to lack of efficacy	n	5	2	2	-	9 (5.5)
Completed	**n**	**97 (95.1)**	**21 (91.3)**	**18 (90.0)**	**19 (100)**	**155 (94.5)**
Full Analysis Set (FAS)	n (%)	97 (95.1)	21 (91.3)	18 (90.0)	19 (100)	155 (94.5)
Per Protocol Set (PPS)	n (%)	82 (80.4)	14 (60.9)	14 (70.0)	16 (84.2)	126 (76.8)
Safety set	n (%)	102 (100)	23 (100)	20 (100)	19 (100)	164 (100)

n number of assessable patients; Percentage calculated as percentage of the randomised patients

The main demographic data and baseline characteristics are presented in Tables 3 and 4.

Patients were mostly Caucasian (95.7%) and mainly male (64.0%), with a mean age (± SD) of 56.2 ± 6.9 years. The mean duration of type 2 diabetes was 72.9 ± 57.9 months, *i.e.* about 6 years (median about 5 years).

All patients reported being on diet for ≥ 3 months, and most (76.8%) were treated with an OAD. Mean BMI was 30.7 ± 4.1 kg/m², and most patients did not smoke (75.6%) or drink alcohol (61.6%). Other relevant medical and surgical history, related to type 2 diabetes included hypertension (64.6%), dyslipidaemia (48.8%), microvascular complications (7.9%) and macrovascular complications (7.3%). No clinically relevant between-group differences were observed.

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SUMMARY – CONCLUSIONS (Cont'd)

STUDY POPULATION AND OUTCOME (Cont'd)

No relevant between-group differences were detected for efficacy parameters at baseline (D0). The mean FPG was 10.4 ± 2.2 mmol/L, and plasma glucose profile was similar in all treatment groups. Mean HbA1c was 7.8 ± 0.7%.

Table 3 - Main demographic and characteristics at baseline in the S 44497 groups in the Randomised Set

Baseline characteristics		**S 44497**				
		50 mg (N = 21)	**100 mg (N = 19)**	**150 mg (N = 20)**	**200 mg (N = 23)**	**300 mg (N = 19)**
Age (years)	Mean ± SD	56.7 ± 5.0	57.7 ± 5.1	54.2 ± 7.3	57.9 ± 7.0	54.4 ± 9.3
	Min - Max	43 – 63	48 – 65	39 – 65	38 – 65	35 – 65
Males	n (%)	14 (66.7)	9 (47.4)	14 (70.0)	12 (52.2)	15 (79.0)
Caucasians	n (%)	20 (95.2)	18 (94.7)	20 (100.0)	22 (95.7)	19 (100.0)
BMI (kg/m^2)	Mean ± SD	30.7 ± 3.7	29.0 ± 3.7	29.8 ± 4.6	31.3 ± 3.9	30.9 ± 4.7
	Min - Max	25.1 – 38.0	24.4 – 37.4	21.7 – 37.5	24.5 – 37.5	23.4 – 37.4
Duration of diabetes	Mean ± SD	69.0 ± 58.4	74.7 ± 42.7	57.8 ± 38.6	82.1 ± 63.3	66.4 ± 51.5
(months)	Min - Max	9 – 257	4 – 162	7 – 157	4 – 238	7 – 164
FPG (mmol/L)	Mean ± SD	10.2 ± 2.0	10.0 ± 1.9	10.2 ± 2.1	10.9 ± 2.7	10.3 ± 1.9
	Min - Max	7.2 – 15.1	7.6 – 13.1	6.7 – 13.3	7.4 – 17.4	7.4 – 14.4
HbA1c (%)	Mean ± SD	7.8 ± 0.6	7.6 ± 0.5	8.0 ± 0.8	7.8 ± 0.6	8.0 ± 0.7
	Min - Max	6.8 – 9.2	6.9 – 8.6	6.8 – 9.4	7.0 – 9.0	6.6 – 8.9

n Number of assessable patients; *Percentage calculated as percentage of the randomised patients; BMI body mass index*

Table 4 - Main demographic and characteristics at baseline in the comparator groups in the Randomised Set

Baseline characteristics		**Placebo (N = 23)**	**Sitagliptin (N = 20)**	**Glimepiride (N = 19)**	**All (N = 164)**
Age (years)	Mean ± SD	56.3 ± 7.4	55.4 ± 7.0	56.8 ± 6.6	56.2 ± 6.9
	Min - Max	41 - 65	39 - 65	40 - 64	35 - 65
Males	n (%)	15 (65.2)	14 (70.0)	12 (63.2)	105 (64.0)
Caucasians	n (%)	22 (95.7)	18 (90.0)	18 (94.7)	157 (95.7)
BMI (kg/m^2)	Mean ± SD	30.8 ± 3.8	32.8 ± 3.6	30.3 ± 4.4	30.7 ± 4.1
	Min - Max	22.1 - 37.0	26.6 - 38.3	23.6 - 37.7	21.7 - 38.3
Duration of diabetes	Mean ± SD	71.0 ± 50.2	87.3 ± 77.6	73.7 ± 74.3	72.9 ± 57.9
(months)	Min - Max	5 - 226	5 - 346	9 - 344	4 - 346
FPG (mmol/L)	Mean ± SD	10.5 ± 2.1	10.3 ± 2.6	10.4 ± 1.9	10.4 ± 2.2
	Min - Max	6.7 - 14.5	7.1 - 16.4	7.3 - 14.2	6.7 - 17.4
HbA1c (%)	Mean ± SD	7.7 ± 0.7	8.1 ± 0.9	7.6 ± 0.7	7.8 ± 0.7
	Min - Max	6.6 - 9.5	6.9 - 9.8	6.4 - 8.9	6.4 - 9.8

n Number of assessable patients; Percentage calculated as percentage of the randomised patients; BMI body mass index

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SUMMARY – CONCLUSIONS (cont'd)

STUDY OUTCOME (cont'd)

In the FAS, results obtained were similar to those obtained in the Randomised Set.

During the study, in the FAS, treatment duration ranged between 23 and 30 days with a mean (± SD) of 27.8 ± 0.7 days and mean global compliance was good 101%, ranging from 96% to 107%. No relevant between-group difference was observed.

The main PK results at steady-state (Day 28) are summarised below.

Table 5 - Main pharmacokinetic parameters of S 44497 in plasma after oral administration on D28

	Dose group	50 mg	100 mg	150 mg	200 mg	300 mg
$t_{max, ss}$ (h)	n	18	18	20	21	18
	Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min - Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
$C_{av,ss}$ (ng/mL)	n	13	17	19	20	17
	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min - Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
$C_{max, ss}$ (ng/mL)	n	18	18	20	21	18
	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min - Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
$AUC_{last, ss}$ (ng.h/mL)	n	18	18	20	21	18
	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min - Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

$t_{max\ ss}$ *Time of maximum plasma concentration at steady-state*

$C_{av\ ss}$ *Average concentration at steady-state*

$C_{max\ ss}$ *maximum plasma concentration at steady-state*

$AUC_{last\ ss}$ *Area under the plasma concentration versus time curve from the time of administration to the last measurable plasma concentration at steady-state*

EFFICACY RESULTS

- **Primary efficacy criterion: plasma glucose profile (AUC 0-24 hours)**

Main analysis: change in plasma glucose profile from baseline to D28 in the FAS (S 44497 *versus* placebo)

In all the S 44497 groups, the mean glucose profiles (AUC_{0-24h}) were decreased at D28 compared to baseline, with a change which appeared dose-related over the range 50-300 mg/day (from -4.6 ± 32.4 mmol/L·h to -26.0 ± 46.1 mmol/L·h, respectively) (Table 5). In the placebo group, the change was negligible (-1.3 ± 45.6 mmol/L·h). There was a statistically significant difference between S 44497 100-300 mg groups *versus* placebo group in favour of S 44497 groups.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

The difference in mean weighted AUC (*i.e.* $AUC_{0\text{-}24h}$ divided by 24) from baseline to D28 was in the S 44497 groups: -0.19 ± 1.35 mmol/L (50 mg), -0.85 ± 1.16 mmol/L (100 mg), -0.83 ± 1.31 mmol/L (150 mg), -1.11 ± 1.02 mmol/L (200 mg), -1.08 ± 1.92 mmol/L (300 mg) and -0.05 ± 1.90 mmol/L in the placebo group.
Robustness analyses showed similar results. In the PPS, similar results were observed for plasma glucose $AUC_{0\text{-}24h}$ except that the mean decrease from baseline to D28 was greater in the S 44497 300 mg group than in the 200 mg group.

Table 6 - Plasma glucose profiles (0-24h) - Change from baseline value to D28 - S 44497 *versus* placebo in the FAS (N = 155): AUC (0-24h) and WAUC

Plasma glucose		**S 44497**					**Placebo**
Visit		**50 mg (N = 19)**	**100 mg (N = 19)**	**150 mg (N = 20)**	**200 mg (N = 21)**	**300 mg (N = 18)**	**(N = 21)**
AUC 0-24h (mmol/L·h)							
Baseline	Mean ± SD	268.4 ± 50.1	271.7 ± 57.8	265.3 ± 58.3	264.8 ± 57.6	271.2 ± 57.5	281.0 ± 82.3
	Median	256.8	260.4	264.0	252.9	263.0	289.7
	Min - Max	186 - 391	189 - 375	163 - 400	197 - 387	194 - 395	169 - 487
D28 - Baseline							
	Mean ± SD	-4.6 ± 32.4	-20 3 ± 27.8	-19.8 ± 31.5	-26.7 ± 24.4	-26.0 ± 46.1	-1.3 ± 45.6
	Median	-5.9	-20.9	-19.5	-28.9	-35.5	8.2
	Min - Max	-47 - 69	-60 - 49	-86 - 55	-74 - 17	-89 - 100	-101 - 103
Statistical analysis (multiple comparisons)*							
S 44497 *versus* placebo							
.	E (SE)	-6.6 (10.6)	-22.8 (10.7)	-23.1 (10.4)	-30.9 (10.3)	-28 5 (10.7)	
	95% CI	[-27.6 ; 14.4]	[-43.9 ; -1.6]	[-43.8 ; -2.4]	[-51.4 ; -10.4]	[-49.8 ; -7 2]	
WAUC (mmol/L)							
Baseline	Mean ± SD	11.18 ± 2.09	11.32 ± 2.41	11.06 ± 2.43	11.03 ± 2.40	11.30 ± 2.40	11.71 ± 3.43
	Median	10.70	10.85	11.00	10.54	10.96	12.07
	Min - Max	7.74 – 16.29	7.88 – 15.61	6.77 – 16.66	8 21 – 16.12	8.07 – 16.47	7.06 – 20.27
D28 - Baseline							
	Mean ± SD	-0.19 ± 1.35	-0.85 ± 1.16	-0.83 ± 1.31	-1.11 ± 1.02	-1.08 ± 1 92	-0.05 ± 1.90
	Median	-0.24	-0.87	-0.81	-1.20	-1.48	0.34
	Min - Max	-1.97 - 2.89	-2.48 - 2.03	-3.58 - 2.27	-3.10 - 0.71	-3.71 - 4.18	-4.22 - 4.30
Statistical analysis (multiple comparisons)*							
S 44497 *versus* placebo							
.	E (SE)	-0.27 (0.44)	-0.95 (0.44)	-0.96 (0.43)	-1.29 (0.43)	-1.19 (0.45)	
	95% CI	[-1.15; 0.60]	[-1.83; -0.07]	[-1.83; -0.10]	[-2.14; -0.43]	[-2.07; -0.30]	

*Baseline last value before study treatment administration; * General linear model adjusted on baseline and centre (fixed effect), with estimates (E) and Standard errors (SE) of differences between group (S 44497 minus placebo) means; 95% CI 95% Confidence interval of the estimate; WAUC weighted AUC*

Change in plasma glucose profile from baseline to D28 in the FAS (S 44497 *versus* sitagliptin and glimepiride)

For the active comparators, the mean decreases in glucose $AUC_{0\text{-}24h}$ over the treatment period were -24.8 ± 36.7 mmol/L·h (median: -25.3) in the sitagliptin group and -72.7 ± 35.8 mmol/L·h (median: –66.5) in the glimepiride group. Compared to the S 44497 doses, there were no statistically significant differences in change *versus* sitagliptin, but a significant differences were detected in the comparisons *versus* glimepiride (favouring glimepiride): E [95% CI]: 50 mg: 61.9 [41.7 ; 82.2]; 100 mg: 46.0 [25.8 ; 66.3]; 150 mg: 46.6 [26.4 ; 66.7]; 200 mg: 39.2 [19.3 ; 59.1]; 300 mg: 40.9 [20.3 ; 61.5]).
The difference in mean weighted AUC from baseline to D28 was -1.03 ± 1.53 mmol/L in the sitagliptin group and -3.03 ± 1.49 mmol/L in the glimepiride group.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Change in post-prandial glucose profile from baseline to D28

In general, there was a decrease in the AUCs over each post-prandial interval, over the treatment period in the S 44497 groups with a trend towards a dose effect after breakfast (Table 6) and after lunch, in the FAS. The mean changes in the S 44497 groups (for each dose) were greater than in the placebo group for each post-prandial interval, except for one comparison ($AUC_{11\text{-}14h}$: S 44497 50 mg *versus* placebo). There were no statistical differences between the mean values of $AUC_{0\text{-}4h}$ in the S 44497 *versus* placebo groups (except S 44497 200 mg *versus* placebo group), but statistically significant differences between S 44497 100-300 mg groups *versus* placebo group, considering $AUC_{4\text{-}7h}$.

No statistical difference between S 44497 *versus* sitagliptin group was detected. In the glimepiride group, the mean decreases in the AUCs at D28 were: -16.3 ± 8.9 mmol/L·h for $AUC_{0\text{-}4h}$, -11.7 ± 6.9 mmol/L·h for $AUC_{4\text{-}7h}$ *versus* -7.9 ± 5.9 mmol/L·h $AUC_{11\text{-}14h}$. These changes were statistically significantly greater in each post-prandial interval than were observed for the S 44497 groups.

Table 7 - Post-prandial glucose profile (AUC 0-4h) - Change from baseline to D28
S 44497 *versus* placebo in the FAS (N = 155)

Post-prandial glucose		**S 44497**					**Placebo**
AUC (mmol/L·h)		**50 mg**	**100 mg**	**150 mg**	**200 mg**	**300 mg**	
Visit		**(N = 19)**	**(N = 19)**	**(N = 20)**	**(N = 21)**	**(N = 18)**	**(N = 21)**
Baseline	n	19	19	20	21	18	21
	Mean ± SD	55.6 ± 10.5	52.7 ± 13.3	52.6 ± 14.9	52.0 ± 13.2	53.3 ± 12.8	55.0 ± 17.5
	Min - Max	33.5 - 69.3	31.8 - 78.6	27.6 - 87.0	35.1 - 75.4	33.8 - 79.5	29.6 - 79.5
D28 - Baseline	n	19	19	20	21	18	21
	Mean ± SD	-2.9 ± 8.2	-4.9 ± 8.1	-4.4 ± 6.7	-6.0 ± 8.8	-3.6 ± 11.0	-0.4 ± 9.6
	Min - Max	-20.9 - 10.1	-16.8 - 18.6	-16.9 - 8.2	-27.6 - 8.3	-22.7 - 23.3	-13.9 - 27.9
Statistical analysis (multiple comparisons)*							
S 44497 *versus* placebo							
	E (SE) (1)	-2.4 (2.7)	-5.0 (2.7)	-4.6 (2.7)	-6.3 (2.6)	-3.8 (2.7)	
	95% CI (2)	[-7.8 ; 2.9]	[-10.3 ; 0.4]	[-9.9 ; 0.6]	[-11.5 ; -1.1]	[-9.2 ; 1.6]	

** General linear model adjusted on baseline and centre (fixed effect), with estimates (E) and Standard errors (SE) of differences between group means (S 44497 minus placebo); 95% CI 95% Confidence interval of the estimate; Baseline last value before study treatment administration; n number of assessable patients*

- **Secondary criteria**

Note: only the results in the FAS are discussed, but the results in the PPS were found to be similar.

Fasting plasma glucose

At D29, the mean FPG (in the FAS) was around 10 mmol/L in the S 44497 groups (50 mg: 10.0 ± 1.8 mmol/L, 100 mg: 9.4 ± 2.1 mmol/L, 150 mg: 9.2 ± 1.6 mmol/L, 200 mg: 9.5 ± 1.8 mmol/L, 300 mg: 9.2 ± 1.8 mmol/L). The lowest mean FPG value was in the glimepiride group (8.0 ± 1.7 mmol/L). The mean FPG decreased in all groups during the study (maximum in the S 44497 for dose 200 mg: -1.1 ± 1.6 mmol/L), except in the S 44497 50 mg group (0.2 ± 1.1 mmol/L) and in the placebo group (0.3 ± 1.9 mmol/L). The decrease in mean FPG was similar in the S 44497 150-300 mg and sitagliptin group (-0.9 ± 1.5 mmol/L). The mean decrease was highest in the glimepiride group (-2.4 ± 1.4 mmol/L).

Post-prandial glucose excursion

The mean changes in post-prandial glucose excursions over the treatment period (D28 minus baseline) indicated favourable changes in the S 44497 groups. There was a decrease in the Post-Prandial Glucose levels at 2 hours after breakfast over the treatment period in all groups except in the placebo group (-0.2 ± 3.1 mmol/L). In the S 44497 groups, the decrease over treatment period ranged between -0.8 ± 3.6 mmol/L and -2.2 ± 3.0 mmol/L. In the sitagliptin group, the change was -2.5 ± 3.5 mmol/L and in the glimepiride group, it was -4.5 ± 2.5 mmol/L (unplanned analysis).

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

HbA1c

The mean HbA1c (in the FAS) decreased in all groups during the study except in the placebo group (0.1 ± 0.6%). Mean changes were similar in the S 44497 groups (50 mg: -0.2 ± 0.5%, 100 mg: -0.1 ± 0.6%, 150 mg: -0.4 ± 0.4%, 200 mg: -0.1 ± 0.5%, 300 mg: -0.3 ± 0.4%) in comparison with sitagliptin and glimepiride groups (-0.3 ± 0.4% and -0.3 ± 0.5%, respectively).

Post-prandial insulin profile

The inter-individual variability in plasma insulin levels was high. In the S 44497 groups 50-200 mg, there was a mean increase from baseline to D28 in insulin $AUC_{0\text{-}4h}$, with a trend towards a greater change with increasing dose from 50 to 150 mg, (Table 8), but with a reduction *versus* baseline in the 300 mg dose group. No statistical between-group differences (S 44497 *versus* placebo or sitagliptin) were detected. In the sitagliptin group the mean increase was 155.0 ± 268.7 pmol/L·h. In the glimepiride group, the mean increase from baseline to D28 (317.3 ± 334.3 pmol/L·h) was higher than in any gliptin group and the between-group differences in change *versus* the S 44497 50, 100, and 300 mg groups were statistically significant.

Table 8 - Post-prandial insulin profile (AUC 0-4h) - Change from baseline to D28
S 44497 *versus* placebo in the FAS (N = 155)

	S 44497					Placebo
AUC (0-4h) (pmol/L·h)	**50 mg (N = 19)**	**100 mg (N = 19)**	**150 mg (N = 20)**	**200 mg (N = 21)**	**300 mg (N = 18)**	**(N = 21)**
Baseline						
Mean ± SD	801.8 ± 533.9	999.6 ± 988.0	587.7 ± 304.2	795.0 ± 444.9	883.6 ± 618.7	742.5 ± 416.1
Median	612.6	750.5	523.0	721.8	584.1	717.4
Min - Max	217.5 - 2155.0	90.4 - 4314.0	174.1 - 1216.4	172.6 - 1685.6	258.8 - 2160.4	232.4 - 1819.3
D28 - Baseline						
Mean ± SD	6.5 ± 236.3	66.9 ± 340.7	132.7 ± 95.9	117.4 ± 373.3	-27.2 ± 322.6	47.3 ± 161.1
Median	18.2	31.1	110.7	53.4	-116.8	47.1
Min - Max	-480.1 - 444.5	-560.0 - 850.5	-18.8 - 281.5	-363.1 - 1085.3	-630.8 - 573.8	-313.6 - 337.6
Statistical analysis						
S 44497 *versus* placebo						
E (SE) [(1)]	-47.6 (94.4)	8.08 (94 3)	119.5 (98.3)	70.2 (92.2)	-74.4 (98.2)	
95% CI [(2)]	[-235.2 ; 140.1]	[-179.5 ; 195.7]	[-76.0 ; 315.0]	[-113.2 ; 253.6]	[-269.7 ; 120.9]	

** General linear model adjusted on baseline and centre (fixed effect), with estimates (E) and Standard errors (SE) of differences between group means (S 44497 minus placebo); 95% CI 95% Confidence interval of the estimate; Baseline last value before study treatment administration; n number of assessable patients*

Post-prandial C-peptide profile

The post-prandial C-peptide $AUC_{0\text{-}4h}$ was slightly increased at D28 compared to baseline in all active groups and was stable in the placebo group. There was no statistically significant difference in mean C-peptide $AUC_{0\text{-}4h}$, or $AUC_{11\text{-}14h}$ between S 44497 *versus* placebo or sitagliptin group. There was a statistically significant difference (S 44497 *versus* glimepiride) on $AUC_{0\text{-}4h}$ in favour of glimepiride, and a statistically significant difference on $AUC_{11\text{-}14h}$, in favour of glimepiride *versus* S 44497 50 mg and 300 mg groups.

Post-prandial GLP-1 profile

The GLP-1 $AUC_{0\text{-}4h}$ increased at D28 compared to baseline in the S 44497 and sitagliptin groups while it decreased in the placebo and glimepiride groups, (S 44497 50 mg group: 9.3 ± 12.5 pmol/L·h, 100 mg: 24.3 ± 19.2 pmol/L·h, 150 mg: 26.5 ± 21.8 pmol/L·h, 200 mg: 22.7 ± 10.1 pmol/L·h, 300 mg: 22.0 ± 12.5 pmol/L·h, sitagliptin: 26.5 ± 11.6 pmol/L·h, placebo: -2.7 ± 5.9 pmol/L·h, glimepiride: -0.9 ± 6.4 pmol/L·h).

The between-group difference was statistically significant in favour of S 44497 *versus* placebo, as well as for the $AUC_{11\text{-}14h}$ (except the S 44497 50 mg group). There was no statistically significant difference between S 44497 *versus* sitagliptin, except for the S 44497 50 mg group in favour of sitagliptin group.

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SUMMARY – CONCLUSIONS (Cont'd)

EFFICACY RESULTS (Cont'd)

Post-prandial glucagon profile

The glucagon $AUC_{0\text{-}4h}$ decreased at D28 compared to baseline in all groups except in the glimepiride group, in the FAS. There was no statistically significant difference between S 44497 groups *versus* placebo, sitagliptin, or glimepiride groups.

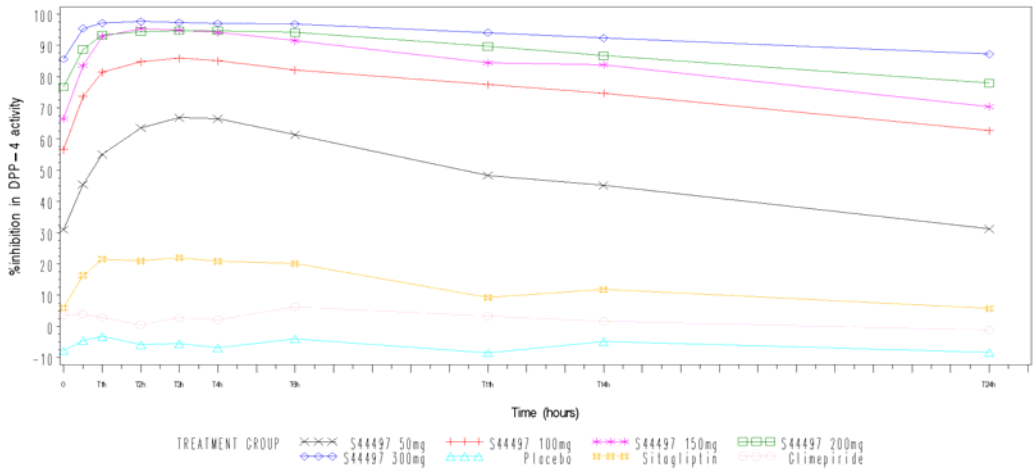
DPP-4 inhibition

The DPP-4 inhibition was dose-related in the S 44497 groups over the range 50-300 mg, and greater at D28 than at D1. At D1, in the S 44497 groups 150, 200 and 300 mg the mean was > 85% inhibition 2 hours (T2) following the intake of study drug. At D28, 85% inhibition was attained in the S 44497 200 and 300 mg groups at 30 min (T0.5), and in the 100 and 150 mg groups at 3 hours (T3) following the intake of study drug.

At D1, the mean trough reached (24h) were from 28.5% to 79.0% in the S 44497 50 to 300 mg group, and were over 65.0% for 150 to 300 mg group, and at D28, 31.3% to 87.2% in the S 44497 50 to 300 mg group. The mean trough inhibition at D28 was over 80% only for 300 mg group.

As expected, no inhibition of DPP-4 activity was observed in either the placebo or the glimepiride groups. In the sitagliptin group at D1, the maximal mean inhibition was 24.3 ± 10.7% at T2; at D28 it was 21.6 ± 12.8% at T1. These unexpectedly low results appeared to be due to the dilution of the plasma as part of the assay procedure, for which the sitagliptin samples appear more sensitive than the S 44497 samples. Using a revised dilution (1:2.5) the inhibition of DPP-4 by sitagliptin was 90%.

Figure 1 - DPP-4 inhibition profile at D28



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SAFETY RESULTS

Table 9 - Summary of safety results

	S 44497						Placebo	Sitagliptin	Glimepiride
	50 mg (N = 21)	100 mg (N = 19)	150 mg (N = 20)	200 mg (N = 23)	300 mg (N = 19)	Pool (N = 102)	(N = 23)	(N = 20)	(N = 19)
Patients	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Having reported at least one:									
EAE	6 (28.6)	7 (36.8)	7 (35.0)	6 (26.1)	3 (15.8)	29 (28.4)	9 (39.1)	5 (25.0)	8 (42.1)
Treatment-related EAE	3 (14.3)	4 (21.1)	4 (20.0)	2 (8.7)	1 (5.3)	14 (13.7)	2 (8.7)	1 (5.0)	6 (31.6)
Serious AE (including death)	-	-	-	-	-	-	-	-	-
Withdrawn due to AE	-	-	-	-	-	-	-	-	-

n number of assessable patients; Percentage calculated as percentage of the randomised patients from the Safety Set

Overall 51 patients (31.1%) reported 90 **emergent adverse events** during the study, with no relevant between-group difference. The incidence of emergent adverse events was 28.4% in the pooled S 44497 group (28.6% in the 50 mg, 36.8% in the 100 mg, 35.0% in the 150 mg, 26.1% in the 200 mg, and 15.8% in the 300 mg group).
In the S 44497 pooled group, the most frequently affected system organ classes (SOCs) were *gastrointestinal disorders* (9 patients, 8.8%), *infections and infestations* (7 patients, 6.9%), and *nervous system disorders* (6 patients, 5.9%). In the comparator groups, the most frequent SOC was *infections and infestations*: 3 patients (13.0%) in the placebo group, 2 patients (10.0%) in the sitagliptin group and 3 patients (15.8%) in the glimperide group. There were also 2 patients (10.0%) in the sitagliptin group with adverse events in the SOC v*ascular disorders* (10.0%).
In the S 44497 pooled group, the most frequent emergent adverse events were nasopharyngitis (6 patients, 5.9%) and headache (3 patients, 2.9%). No dose effect appeared in the S 44497 groups. Emergent hypoglycaemia was more frequently reported in the glimepiride group than in other groups. According to classification of hypoglycaemia by European Medicines Agency, the distribution was as follows: 1 suggestive episode in each of the S 44497 100 mg and placebo groups; 1 patient with 1 suggestive episode and 1 patient with 8 confirmed episodes in the glimepiride group. No major hypoglycaemia occurred.
Emergent adverse events were rated either as mild (73.3%) or moderate intensity (26.7%). None were rated as severe.
Treatment-related emergent adverse events according to investigator were reported in 23 patients: 14 patients (13.7%) in the S 44497 pooled group with no dose-effect, 2 patients (8.7%) in the placebo group, 1 patient (5.0%) in the sitagliptin group, and 6 patients (31.6%) in the glimepiride group. No particular SOC was affected by treatment-related emergent adverse events in the treatment groups, except *metabolism and nutrition disorders* in the glimepiride group due to hypoglycaemia.
Most (90.0%) of the emergent adverse events recovered; 6 were not recovered by the last follow-up visit (vitreous floaters in the S 44497 100 mg group, transaminases increased and uterine polyp in the S 44497 150 mg group, contusion and choroidal effusion in the S 44497 200 mg group, and flatulence in the sitagliptin group, none except flatulence was considered as treatment-related).
No patient died during the study, experienced any serious adverse event, or had any adverse event which led to premature treatment withdrawal.

Biochemistry and haematology parameters did not show any clinically relevant mean changes over the treatment period or relevant differences between groups.

Vital signs
Body weight slightly decreased over time (less than 1 kg) in all groups except in the sitagliptin and glimepiride groups. Mean change was higher in the S 44497 50 mg and 150 mg group than in the placebo group: -0.8 ± 1.5 kg and -0.7 ± 1.5 kg *versus* -0.1 ± 1.4 kg, respectively. A mean decrease over the study was observed in most groups for sitting blood pressure (SBP and DBP) and heart rate.

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SAFETY RESULTS (Cont'd)

ECG

Among the ECG abnormalities reported during the study (47 at baseline and 43 at D28), one case of atrial fibrillation at D28 (S 44497 50 mg group) was considered clinically significant. This was reported as a treatment-related adverse event of mild intensity, not serious, and which recovered.

CONCLUSION

In conclusion, in patients with type 2 diabetes treated over a 4-week period, S 44497 (50 - 300 mg/day) dose-dependently decreased mean 24-hour plasma glucose profile (primary criterion). The difference in change *versus* placebo was statistically significant for dose groups 100, 150, 200 and 300 mg. The efficacy of sitagliptin 100 mg appeared between that of S 44497 150 and 200 mg on the primary criterion. No statistically significant between-group difference (S 44497 *versus* sitagliptin) was detected. The efficacy of glimepiride 2-4 mg on the primary criterion was superior to S 44497 and sitagliptin, with a statistically significant between-group (S 44497 *versus* glimepiride) difference.

Analyses of the secondary efficacy criteria confirmed antihyperglycaemic effects of S 44497 and the results were consistent with its proposed mechanism of action. No particular safety concerns were detected in patients treated with S 44497.

Date of the report: 22 July 2010