STUDY SUMMARY SHEET- TABULATED STUDY REPORT

Name of Company: **I.R.I.S.** **50 rue Carnot** **92284 Suresnes Cedex - FRANCE**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product:	**Volume:**	
Name of Active Ingredient: Gliclazide MR and metformin IR **S 05720A (bilayer tablet)**	**Page:**	

Title of study:
A pilot single dose study to compare the *in vivo* release profiles from three fixed combination (gliclazide modified release (MR) 60 mg/metformin immediate release (IR) 1000 mg) tablets, varying by their *in vitro* release rates, with the free combination (gliclazide MR 60 mg tablet and metformin IR 1000 mg tablet), and a 60 mg gliclazide oral solution.
Single dose, open-label, modified randomised (five-period) four-way crossover study in healthy male volunteers.
Protocol No.:**PKH-05720-001**

Persons involved in the study:
- **Clinical Investigator:** [redacted]
- **Analytical centre (gliclazide and metformin assays):** [redacted]
- **Data management, coding, statistical analysis (safety), medical writing (clinics):** [redacted]
- **Pharmacokinetic analysis:** [redacted]

Publication (reference): Not applicable (NA)

Studied period:	**Phase of development of the study:**
Initiation date: 21 September 2010 Completion date: 29 November 2010	Phase 1

Objective(s):
Primary objectives: To compare the *in vivo* release profiles from three fixed combination (gliclazide MR 60 mg/metformin IR 1000 mg tablet), varying by their *in vitro* release rates, with the free combination (gliclazide MR 60 mg tablet and metformin IR 1000 mg tablet), and a 60 mg gliclazide oral solution after single oral administration.
Secondary objective: To collect information on safety and tolerability of the fixed combination.

Methodology:
Single-centre, single dose, open-label, modified randomised crossover study.
First period with single oral administration of a 60 mg gliclazide oral solution, followed by a randomized four-way crossover design with single oral administration of the free fixed combination (gliclazide MR 60 mg/metformin IR 1000 mg) tablets varying by their in vitro release rates and the free combination (gliclazide MR 60 mg tablet and metformin IR 1000 mg tablet).

Number of Participants:
Planned: 12 completed subjects as a minimum (16 to be included)
Included: 16 subjects were included and 14 completed the study
Assessable for pharmacokinetics: 16 subjects.

Main criteria for inclusion:
Healthy male Caucasian volunteers aged between 18 and 40 years old inclusive with a body mass index (BMI) between 18.5 to 27 kg/m^2 inclusive, who had freely given their written consent to participate in the study. Willing to take and able to swallow a big capsule (DBcap size AAA capsule) as assessed with a placebo capsule.

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Study drug (Test medication):
S 05720A, fixed combination (gliclazide MR 60mg /metformin IR 1000 mg) tablets varying by their *in vitro* release rates (Slow, Medium and Quick).
Batch numbers: Slow L0034979, Medium L0034987, Quick L0034981.

Reference product:
Gliclazide 60 mg oral solution, batch number: L003415
Free combination, gliclazide MR 60 mg tablet, batch number: L0034995 and metformin IR 1000 mg tablet batch number L0034064.

Duration of treatment:
Five (5) single oral administrations of either gliclazide oral solution, or the fixed combinations, or the free combination with a washout period of at least 10 days was performed between each administration.
Study duration of a participant lasted approximately 12 weeks, from screening (ASSE) to end-of-study visit (RUNO). Screening examination was performed within 2 weeks prior to the first administration. End-of-study examination was performed within 3 to 5 days following the last blood pharmacokinetic sample of the last period.

Criteria for evaluation:

Pharmacokinetic measurements:
- Blood samples were collected just prior dosing, 30 min, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, 10 h, 16 h, 24 h, 36 h, 48 h, and 72 h after dosing for determination of plasma gliclazide and metformin concentrations when applicable.
- Bioanalytical assay: The analyses were based on protein precipitation and LC separation with MS-MS detection. This method allowed the analysis of gliclazide and metformin from 50 µL of plasma within the concentration ranges 5.00 to 2500 ng/mL and 10.0 to 5000 ng/mL, respectively. The LLOQ were 5.0ng/mL and 10 ng/mL for gliclazide and metformin, respectively.
- Pharmacokinetic parameters were calculated from the individual plasma concentration-time data using non-compartmental techniques and actual sampling and administration times and the bioequivalence analysis was performed using the Bioequivalence Wizard in WinNonlin (WinNonlin™ Professional Network Edition, Version 5.2, Pharsight Corp, Palo Alto, CA).

Safety measurements:
- Physical examination including vital signs, electrocardiogram, laboratory analysis, adverse events follow-up were performed.
- A specific procedure was performed in order to prevent hypoglycaemia: a solution of 5% glucose was infused with adjustment of the infusion rate according to measured blood glucose.

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Name of Active Ingredient: Gliclazide MR and metformin IR **S 05720A (bilayer tablet)**	**Page:**	

SUMMARY - CONCLUSIONS

STUDY POPULATION OUTCOME

A total of 27 subjects were screened. Among them, 20 were selected and 16 were included in the study (14 subjects in conformity with the protocol, and 2 with protocol deviation before or at inclusion). Fourteen (14) included subjects completed the study, 2 included subjects withdrew due to non medical reason.
Sixteen (16) subjects constituted the Randomised Set, the Safety Set and the Pharmacokinetic Set.
This study was performed according to protocol PKH-05720-001, no clinically relevant deviation, abnormality or medical history was observed that would have interfered with the study investigations.

MAIN CHARACTERISTICS OF THE RANDOMISED SET

All subjects (n=16) were male, Caucasian, with mean age ± SD 26.8 ± 6.5 years, mean weight ± SD 74.3 ± 8.3 kg, mean height ± SD 180.8 ± 7.1 cm, mean BMI ± SD 22.7 ± 1.5 kg/cm^2.

PHARMACOKINETIC RESULTS:

Main gliclazide PK parameters (geometric mean (%CV)).

		Treatment				
Parameter	**Unit**	**Free Combination (N=14)**	**Slow Release (N=15)**	**Medium Release (N=15)**	**Quick Release (N=15)**	**60 mg Oral Solution (N=16)**
AUC_{last}	ng.hr/mL	32345 (52.6)	26755 (50.5)	27796 (41.3)	26586 (49.1)	30804 (43.4)
AUC*	ng.hr/mL	29374 (39.6)	25351 (45.3)	26172 (35.8)	24795 (43.6)	28834 (33.4)
C_{max}	ng/mL	1628 (31.4)	1174 (43.9)	1386 (29.2)	1317 (31.7)	2057 (24.3)
$t_{1/2,z}$[2]	hr	15.0 (47.9)	17.2 (66.9)	16.1 (65.9)	17.6 (79.4)	16.1 (54.2)
t_{max}[1]	hr	8.00 (6.00-16.02)	10.00 (6.00-16.00)	10.00 (4.00-24.03)	7.02 (5.00-16.03)	2.00 (2.00-7.00)
t_{lag}[1]	hr	1.00 (0.00-1.02)	1.00 (0.00-1.00)	1.00 (0.00-2.00)	1.00 (0.00-1.02)	0.00 (0.00-0.00)

[1] *median (minimum-maximum),* [2] *arithmetic mean (CV%), * Calculated following exclusion of AUC values with AUC_{ext}>20%, N=12 for free combination, N=13 for slow, medium and quick release fixed combination formulations and N=14 for oral solution.*

- Based on AUC, the gliclazide exposure was 14, 11 and 16% lower for the fixed combination slow, medium and quick formulation, respectively, compared to the free tablet combination.
- The overall exposure of gliclazide, as measured by AUC was, on average, similar across the slow, medium and quick release MR formulations.
- The rate of absorption of gliclazide was slowest for the in vitro slow release fixed combination formulation but the rank order did not follow the predicted release rate and the peak concentrations.

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PHARMACOKINETIC RESULTS:

Main metformin PK parameters (geometric mean (%CV)).

Parameter	Unit	Free Combination (N=14)	Slow Release (N=15)	Medium Release (N=15)	Quick Release (N=15)
AUC_{last}	ng.hr/mL	8814 (20.5)	8576 (24.7)	8688 (20.5)	8959 (21.0)
AUC	ng.hr/mL	8996 (20.4)	9061 (22.0)*	8943 (20.9)	9143 (21.2)
C_{max}	ng/mL	1434 (30.8)	1307 (31.4)	1311 (20.8)	1434 (18.4)
$t_{1/2,z}$ [2]	hr	6.94 (61.7)	10.5 (68.0)*	11.4 (101)	8.43 (71.9)
t_{max} [1]	hr	3.00 (0.50-3.00)	3.00 (2.00-4.00)	3.00 (1.00-4.00)	3.00 (1.00-4.00)
t_{lag} [1]	hr	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)

*[1] median (minimum-maximum), [2] Mean (CV%), * n=14, For Subject ID 8, the slope of apparent terminal elimination could not be estimated due to lack of enough information*

- The overall exposure of metformin as measured by both Cmax and AUCs were, on average, similar across all the four treatments.

Bioequivalence statistical analysis

Compound	Treatment	N	Parameter	Geometric Least Square means (Test/Reference)	Ratio	Lower 90% CI	Upper 90% CI
Gliclazide	Medium Release/Free combination	14	C_{max}	1374/1633	84.12	71.38	99.14
		14	AUC_{last}	27958/31690	88.23	80.98	96.12
Metformin	Medium Release/Free combination	14	C_{max}	1268/1397	90.75	83.01	99.21
		14	AUC_{last}	8484/8694	97.58	92.43	103.02

- For gliclazide, the medium release fixed combination formulation was bioequivalent to the free combination in terms of AUClast but the fixed combination formulation had lower peak gliclazide concentrations resulting in the lower 90% CI for the Cmax ratio being below the acceptance level of 80%.
- For metformin, the medium release fixed combination formulation was bioequivalent to the free combination both in terms of AUClast and Cmax.

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SUMMARY – CONCLUSIONS (cont'd)

SAFETY RESULTS

		Gliclazide oral solution (N=16)	S 05720A SR (N=15)	S 05720A MR (N=15)	S 05720A QR (N=15)	Free combination (N=14)
Subjects having reported						
at least one emergent adverse event	n (%)	11 (68.8)	8 (53.3)	7 (46.7)	8 (53.3)	6 (42.9)
at least one treatment-related emergent adverse event	n (%)	5 (31.3)	1 (6.7)	0 (0)	3 (20.0)	2 (14.3)

'Gliclazide oral solution', 'S 05720A SR', 'S 05720A MR', 'S 05720A QR' and 'Free combination' correspond respectively to '60 mg gliclazide oral solution', 'S 05720A tablet slow release rate', 'S 05720A tablet medium release rate', 'S 05720A tablet quick release rate' and 'Free combination: S 05762 tablet + metformin IR 1000 mg tablet'

A total of 55 mild (49) to moderate (6) EAE occurred in 13/16 subjects (81.3%), of which 11 were considered as treatment-related: headache (3 EAEs in 3 subjects), lethargy (2 EAEs in 2 subjects), diarrhoea (2 EAEs in 1 subject), light-headedness (2 EAEs in 2 subjects) and abdominal discomfort (2 EAEs in 2 subjects), with no clinically relevant difference between treatment groups. All subjects had recovered at the end of the study, except 4 subjects suffering from seasonal allergy. There was no serious AE and no AE required the withdrawal of a subject.

According to the Investigator, no clinically significant change or clinically significant abnormality was observed in laboratory safety parameters, vital signs or ECG records except a mild hypokalaemia after receiving

S 05720A QR.

Despite the specific procedure set-up to prevent the subject from the occurrence of hypoglycaemia, some blood glucose values were low (≤ 3 mmol/L), of which one only was symptomatic. No severe hypoglycaemic episode occurred.

There was no other clinically relevant finding after any treatment administration.

Single administration of S 05720A was well tolerated at any release rate (slow, medium, quick), as were single administrations of reference products (gliclazide oral solution and free combination).

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CONCLUSION:

Pharmacokinetics:

- Gliclazide exposure was similar for the 3 fixed combinations, but lower compared to the free tablet combination.
- The rate of absorption of gliclazide was slowest for the in vitro slow release fixed combination formulations but the rank order did not follow the predicted the in vivo release rate.
- For gliclazide, the medium release fixed combination formulation was bioequivalent to the free combination in terms of AUClast but the Cmax ratio was below the acceptance level of 80%.
- For metformin, the medium release fixed combination formulation was bioequivalent to the free combination both in terms of AUClast and Cmax and both Cmax and AUCs were, on average, similar across all the four treatments.

Safety:

- The S 05720A fixed combination (gliclazide MR 60 mg /metformin IR 1000 mg) bilayer tablet was well tolerated after single oral administration whatever the formulations.

Date of the report: 21 November 2011