AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Dapagliflozin
Study Code	D1691C00002
Edition Number	1
Date	04 August 2010

A two-part, open-label, randomised, single-centre, phase I bioequivalence study comparing (Part I) the fixed dose combination dapagliflozin/metformin IR tablet (2.5 mg/850 mg) versus the free combination of the dapagliflozin tablet (2.5 mg) and metformin IR tablet (850 mg); and (Part II) comparing the fixed dose combination dapagliflozin/metformin IR tablet (5 mg/1000 mg) versus the free combination of the dapagliflozin tablet (5 mg) and metformin IR tablet (1000 mg) in healthy volunteers, both parts in the fed state

Study dates:	First healthy volunteer enrolled: 15 January 2010 Last healthy volunteer completed: 12 April 2010
Phase of development:	Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre

Early Phase Clinical Unit – Berlin, PAREXEL International GmbH, Berlin, Germany.

Study period		Phase of development
First subject enrolled	15 January 2010	I
Last subject completed	12 April 2010	

Publications

None at the time of writing this report

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
Part I: To establish the bioequivalence of a newly formulated FDC dapagliflozin/metformin IR tablet (2.5 mg/850 mg) to the individual dapagliflozin tablet (2.5 mg) and individual metformin IR tablet (850 mg) co-administered.	Cmax, AUC(INF), AUC(0-t) and AUC(0-72)[a] of dapagliflozin and metformin	Pharmacokinetics
Part II: To establish the bioequivalence of a newly formulated FDC dapagliflozin/metformin IR tablet (5 mg/1000 mg) to the individual dapagliflozin tablet (5 mg) and individual metformin IR tablet (1000 mg) co-administered.		
Secondary	**Secondary**	
Description of PK properties (Parts I and II)	Tmax, T-HALF, Tlast and λz of dapagliflozin and metformin	Pharmacokinetics
To examine the safety and tolerability of the combination of dapagliflozin and metformin	Adverse events, laboratory variables, resting 12-lead ECG, vital signs, oral body temperature, body weight and physical examination	Safety

AUC(INF) = area under the plasma concentration-time curve from zero to infinity; AUC(0-t) = area under the plasma concentration-time curve from zero to the time of the last measurable concentration; CSP = Clinical Study Protocol; Cmax = maximum plasma concentration; ECG = electrocardiogram; FDC = fixed dose combination; IR = immediate release; λz = Smallest (slowest) disposition (=hybrid) rate constant; PK = Pharmacokinetics; Tlast = Time at which the last quantifiable plasma concentration was observed; Tmax = time to Cmax; T-HALF = terminal half-life.

a The PK parameter AUC(0-72)was additionally derived due to the fact that derivation of λz, and thus AUC(INF), failed in some subjects based on $R^2 < 0.9$. See also Sections 5.8 and 7.1.4 of the CSR.

Study design

This study was designed as a single-centre, two-part, randomised, open-label, crossover bioequivalence study with 120 healthy volunteers (60 per study part). The first part was a two-way crossover comparing the newly formulated fixed dose combination (FDC) dapagliflozin/metformin immediate-release (IR) 2.5 mg/850 mg tablet to the individual dapagliflozin and metformin IR tablets administered together. The second part was a two-way crossover comparing the newly formulated FDC dapagliflozin/metformin IR 5 mg/1000 mg tablet to the individual dapagliflozin and metformin IR tablets administered together. Part I and Part II were independent of each other, and could be carried out simultaneously.

Target subject population and sample size

A total of 120 (60 per study part) healthy male and female volunteers aged 18 to 45 years, both inclusive. Female volunteers had to be of non-childbearing potential or had to remain abstinent during the clinical study.

Investigational product and comparators: dosage, mode of administration and batch numbers

Drug:	dapagliflozin/metformin
Formulation:	FDC tablet
Route of administration:	oral
Strength:	2.5 mg/850 mg; 5 mg/1000 mg
Dose:	single dose of 2.5 mg/850 mg (Study Part I) and 5 mg/1000 mg (Study Part II)
Batch number:	10-000074AZ (2.5 mg/850 mg); 10-000073AZ (5 mg/1000 mg)

Drug:	dapagliflozin
Formulation:	tablet
Route of administration:	oral
Strength:	2.5 mg; 5 mg
Dose:	single dose of 2.5 mg (Study Part I) and 5 mg (Study Part II)
Batch number:	8E39935 (2.5 mg); 7M21688 (5 mg)

Drug:	Glucophage® (metformin hydrochloride)
Formulation:	tablet
Route of administration:	oral
Strength:	850 mg; 1000 mg
Dose:	single dose of 850 mg (Study Part I) and 1000 mg (Study Part II)
Batch number:	09-006603AZ (850 mg); 09-006602AZ (1000 mg)

Duration of treatment

Part I: Each healthy volunteer received one single dose of FDC dapagliflozin/metformin 2.5 mg/850 mg and one single dose of dapagliflozin 2.5 mg and metformin 850 mg each, separated by a wash-out period of at least seven days.

Part II: Each healthy volunteer received one single dose of FDC dapagliflozin/metformin 5 mg/1000 mg and one single dose of dapagliflozin 5 mg and metformin 1000 mg each, separated by a wash-out period of at least seven days.

Statistical methods

For the primary objectives of Part I and Part II, bioequivalence was demonstrated if the 90% confidence interval (CI) for the formulation effect was contained within the interval of 0.8000–1.2500 for AUC(0-t), AUC(INF), AUC(0-72) and Cmax with respect to both dapagliflozin and metformin.

AUC(0-t), AUC(INF), AUC(0-72) and Cmax were log-transformed prior to analysis. All endpoints were analyzed using an analysis of variance (ANOVA) model for each part separately, with sequence, period and formulation as fixed effects and subject within sequence as a random effect. The results of the analysis were presented in terms of the estimated geometric mean for each formulation with corresponding 95% confidence interval (CI), and the estimated formulation effect (ratio of geometric means) with a 90% CI. Geometric means were estimated by back-transformation of least squares means from the log-transformed data with adjustment for any imbalances in the design. All other pharmacokinetic parameters were summarised by formulation using descriptive statistics only.

Subject population

In total, 120 healthy male and non-fertile female subjects were randomised into the study. Of these, 59 subjects in Part I and 58 subjects in Part II received both IPs and completed the study in accordance with the Clinical Study Protocol. One subject in Part I and 2 subjects in Part II were prematurely discontinued. The safety and the PK analysis sets each included all 120 randomised subjects.

Overall, the treatment groups were well balanced with regards to demographic and baseline characteristics.

Summary of pharmacokinetic results

The results of the bioequivalence comparisons between the FDC tablets of dapagliflozin/metformin 2.5 mg/850 mg and of 5 mg/1000 mg versus the corresponding individual dapagliflozin and metformin IR tablets (free combinations) are shown in Table S2 and Table S3.

The ANOVA of the derived PK variables characterising plasma exposure to dapagliflozin and metformin demonstrated bioequivalence under fed conditions between the FDCs dapagliflozin/metformin (2.5 mg/850 mg) as well as (5 mg/1000 mg) and the free combinations of dapagliflozin + metformin (2.5 mg + 850 mg) and (5 mg + 1000 mg), respectively. The geometric mean ratios of AUC(INF), AUC(0-t), AUC(0-72) and Cmax of both, dapagliflozin and metformin, were very close around unity and the corresponding 90% CIs were all within the pre-defined limits of bioequivalence [0.8:1.25].

Table S2 Bioequivalence comparison between comparison between dapagliflozin 2.5 mg/metformin 850 mg tablet and dapagliflozin 5 mg + metformin 1000 mg, Part I – PK analysis set

Part	Parameter	Unit	Comp.	Test			Reference			Ratio (T:R)	90% CI
				LS mean	N	95% CI	LS mean	N	95% CI	[%]	[%]
I	**Dapagliflozin**										
	AUC(0-t)	ng*h/mL	A vs B	102	60	96.1; 108	100	59	94.5; 106	1.02	0.998; 1.04
	AUC(INF)	ng*h/mL	A vs B	106	51	100; 113	104	52	98.5; 111	1.02	0.996; 1.04
	AUC(0-72)	ng*h/mL	A vs B	102	60	96.1; 108	100	59	94.5; 106	1.02	0.998; 1.04
	Cmax	ng/mL	A vs B	22.3	60	20.9; 23.9	21.7	59	20.2; 23.2	1.03	0.969; 1.10
I	**Metformin**										
	AUC(0-t)	ng*h/mL	A vs B	8128	60	7745; 8531	8122	59	7738; 8526	1.00	0.973; 1.03
	AUC(INF)	ng*h/mL	A vs B	8190	43	7750; 8655	8387	45	7939; 8859	0.977	0.941; 1.01
	AUC(0-72)	ng*h/mL	A vs B	8128	60	7745; 8531	8122	59	7738; 8526	1.00	0.973; 1.03
	Cmax	ng/mL	A vs B	1115	60	1060; 1174	1155	59	1097; 1216	0.966	0.923; 1.01

AUC(INF) = area under the plasma concentration-time curve from zero to infinity; AUC(0-t) = area under the plasma concentration-time curve from zero to the time of the last measurable concentration; $AUC_{(0-72)}$ = area under plasma concentration-time curve from zero to 72 hours and BLOQ after Tlast was not included in the calculation; CI = confidence interval; Comp. = Comparison; LSmean = least-square mean; R = reference; T = test.
Part I: Treatment A - FDC dapagliflozin/metformin 2.5 mg / 850 mg (test); Treatment B - 1 tablet of dapagliflozin 2.5 mg and 1 tablet of metformin IR 850 mg (reference).

Table S3 Bioequivalence comparison between comparison between dapagliflozin 5 mg/metformin 1000 mg tablet and dapagliflozin 5 mg + metformin 1000 mg, Part II – PK analysis set

Part	Parameter	Unit	Comp.	Test			Reference			Ratio (T:R)	90% CI
				LS mean	N	95% CI	LS mean	N	95% CI	[%]	[%]
II	**Dapagliflozin**										
	AUC(0-t)	ng*h/mL	A vs B	223	59	209; 237	224	57	210; 238	0.996	0.975; 1.02
	AUC(INF)	ng*h/mL	A vs B	230	53	216; 246	232	49	218; 248	0.993	0.971; 1.02
	AUC(0-72)	ng*h/mL	A vs B	223	59	209; 237	224	57	210; 238	0.996	0.975; 1.02
	Cmax	ng/mL	A vs B	47.3	59	43.8; 51.0	44.3	57	41.0; 47.9	1.07	0.989; 1.15
II	**Metformin**										
	AUC(0-t)	ng*h/mL	A vs B	9509	59	9012; 10033	9537	58	9038; 10064	0.997	0.970; 1.03
	AUC(INF)	ng*h/mL	A vs B	9374	42	8897; 9877	9506	38	9006; 10035	0.986	0.948; 1.03
	AUC(0-72)	ng*h/mL	A vs B	9509	59	9012; 10033	9537	58	9038; 10064	0.997	0.970; 1.03
	Cmax	ng/mL	A vs B	1312	59	1251; 1377	1310	58	1249; 1375	1.00	0.972; 1.03

AUC(INF) = area under the plasma concentration-time curve from zero to infinity; AUC(0-t) = area under the plasma concentration-time curve from zero to the time of the last measurable concentration; $AUC_{(0-72)}$ = area under plasma concentration-time curve from zero to 72 hours and BLOQ after Tlast was not included in the calculation; CI = confidence interval; Comp. = Comparison; LSmean = least-square mean; R = reference; T = test.

The concentration-time profiles of dapagliflozin and metformin following single administration of the FDCs and the corresponding free tablet combinations were highly similar. Maximum plasma concentrations of dapagliflozin were achieved at a median Tmax between 1.0 and 1.5 hours and geometric mean T-HALF ranged between 11.3 and 15.1 hours across all treatments. Maximum plasma concentrations of metformin were achieved at a median Tmax between 3.0 and 4.0 hours and geometric mean T-HALF ranged between 12.4 and 16.3 hours across all treatments.

Summary of safety results

Overall, 28 (46.7%) of 60 subjects reported a total of 35 AEs in Part I and 24 (40.0%) of 60 subjects reported a total of 38 AEs in Part II during the study. The majority of AEs were of mild intensity, with few AEs of moderate intensity and none of severe intensity. The system organ class most frequently affected in both study parts was gastrointestinal disorders, followed by nervous system disorders and infections and infestations. The most common treatment-emergent AEs in Part I were diarrhoea, headache and nasopharyngitis and in Part II, diarrhoea, headache and nausea.

There were no other significant AEs, no SAEs, no deaths and 1 subject (Part II) was withdrawn due to the occurrence of an AE (abnormal CK value).

Relevant differences between the profiles and the incidences of AEs reported for each treatment did not become evident.

There were no clinically important abnormalities in haematology, clinical chemistry, urinalysis, vital signs, 12-lead ECG recordings and physical examinations in any healthy subject during this study.