Clinical Study Report Synopsis

Drug Substance	Dapagliflozin/metformin
Study Code	D1691C00007
Edition Number	1

EudraCT Number 2013-000169-36

A Bioequivalence Study of the Fixed-dose Combination Dapagliflozin/Metformin Tablet (5 mg/850 mg) Relative to a 5 mg Dapagliflozin Tablet and an 850 mg Metformin (Glucophage® Marketed in Canada by Sanofi-Aventis) Tablet Coadministered to Healthy Volunteers in the Fasted and Fed States

Study dates:	First subject enrolled: 22 April 2013
	Last subject last visit: 02 July 2013
Phase of development:	Clinical pharmacology (I)

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

Study centre(s)

This study was conducted at a single centre in the United Kingdom.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetic	To demonstrate the bioequivalence using the nominal and the potency corrected dosage of a dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet relative to 5 mg dapagliflozin and 850 mg Glucophage® (marketed in Canada by Sanofi-Aventis) tablets administered together in the fasted state in healthy volunteers	Dapagliflozin and metformin AUC, $AUC_{(0-t)}$, and $C_{max.}$
Primary	Pharmacokinetic	To demonstrate the bioequivalence using the nominal and the potency-corrected dosage of a dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet relative to 5 mg dapagliflozin and 850 mg Glucophage tablets administered together in the fed state in healthy volunteers	Dapagliflozin and metformin AUC, $AUC_{(0-t)}$, and $C_{max.}$
Secondary	Pharmacokinetic	To describe the time to reach maximum analyte concentration (t_{max}), time of last quantifiable analyte concentration (t_{last}), terminal rate constant(λ_z), and terminal half-life ($t_{1/2}$) of both dapagliflozin and metformin when administered as an immediate-release fixed-dose combination tablet and as individual tablet components in the fasted state in healthy volunteers	Dapagliflozin and metformin t_{max}, t_{last}, λ_z, and $t_{1/2.}$
Secondary	Pharmacokinetic	To describe the t_{max}, t_{last}, λ_z and $t_{1/2}$ of both dapagliflozin and metformin when administered as an immediate-release fixed-dose combination tablet and as individual tablet components in the fed state in healthy volunteers	Dapagliflozin and metformin t_{max}, t_{last}, λ_z, and $t_{1/2.}$

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Pharmacokinetic	To describe the effect of food on the pharmacokinetic profile (C_{max}, AUC, $AUC_{(0-t)}$, t_{max}, t_{last}, λ_z and elimination $t_{1/2}$ of both dapagliflozin and metformin) of the dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet compared to when administered in the fasted state in healthy volunteers	Dapagliflozin and metformin AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, t_{last}, λ_z, and $t_{1/2}$.
Secondary	Safety	To assess the safety and tolerability of the dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet and of 5 mg dapagliflozin and 850 mg Glucophage administered together in the fasted and fed states in healthy volunteers	Adverse events, clinical laboratory assessments (clinical chemistry, hematology, and urinalysis), physical examination, 12-lead electrocardiogram, and vital signs

Study design

This was an open-label, randomised, 4-period, 4-treatment, 4-way crossover study conducted to determine the bioequivalence of the metformin immediate-release fixed-dose combination tablet of dapagliflozin/metformin (5 mg/850 mg) relative to single tablets of dapagliflozin (5 mg) and metformin (850 mg) Glucophage® (marketed in Canada by Sanofi-Aventis) administered together in healthy volunteers under fasted and fed conditions. At least 36 healthy volunteers were planned for enrolment and random assignment to 1 of 4 treatment sequences according to a William's design for a 4-period, 4-treatment, 4-way crossover study. Treatments included:

- Treatment A: Single oral doses of 5 mg dapagliflozin and 850 mg Glucophage tablets administered together in the fasted state
- Treatment B: A single oral dose of dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet in the fasted state
- Treatment C: Single oral doses of 5 mg dapagliflozin and 850 mg Glucophage tablets administered together in the fed state
- Treatment D: A single oral dose of dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet in the fed state

Treatments A and B were administered in the morning in a fasted state, while Treatments C and D were administered in the morning within 30 minutes of starting a standard high-fat/high-calorie breakfast (fed state). There was at least 5 minutes between completion

of the breakfast and dosing. Serial blood samples for pharmacokinetics analysis of dapagliflozin and metformin were collected over a 72-hour interval following dosing in Treatment Periods 1, 2, 3, and 4 (Visits 2 to 5). The washout between each dose was at least 7 days, but less than 14 days.

Target subject population and sample size

The target population was healthy male and female volunteers aged 18 to 55 years who had a body mass index of between 18.5 and 30 kg/m^2 (inclusive) and weighed at least 50 kg and no more than 100 kg.

At least 36 healthy volunteers were to be enrolled to ensure that 32 healthy volunteers completed the study. A maximum of 40 healthy volunteers could have been enrolled.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers

Investigational product administered to volunteers in this study included dapagliflozin, 5 mg film-coated, immediate-release tablets for oral administration (98.9% drug content, batch number: 9M37268), Glucophage® (marketed in Canada by Sanofi-Aventis) 850 mg immediate-release tablet for oral administration (99% drug content, batch number: 8060933), and dapagliflozin/metformin 5 mg/850 mg film-coated immediate-release, fixed-dose combination table for oral administration (101%/102% drug content; batch number: LL32).

Duration of treatment

The total study duration for each volunteer was approximately 9 weeks. The time from screening and enrolment (Visit 1) to randomisation (Day 1, Visit 2) was a maximum of 28 days. There were 4 treatment periods (Visit 2 to Visit 5) of 5 days each (Day -1 until Day 4). A single, oral dose of the dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet or single, oral doses of each individual tablet were administered under fasted or fed conditions on Day 1 of each treatment period. The washout between each dose was at least 7 days but no longer than 14 days. A follow-up visit (Visit 6) occurred 7 to 10 days following the last dose.

Statistical methods

The analysis was performed using the nominal drug dose and corrected for the measured potency of the administered formulations. Point estimates and 90% confidence intervals for C_{max}, $AUC_{(0-t)}$, and AUC were calculated for the test to reference ratios of geometric means of dapagliflozin and metformin using a linear mixed-effect model. The reference and test treatments were defined as Treatments A and B, respectively, for comparisons within the fasted state, and as Treatments C and D, respectively, for comparisons within the fed state. These estimates were constructed from the results of fitting the linear mixed-effect models for log-transformed data with treatment sequence and period as fixed effects and volunteer within sequence as a random effect. Point estimates of the ratios and their confidence intervals were then transformed back to original scale in order to give point estimates for the ratios of geometric means and their confidence intervals. As per the guidelines from Health Canada,

bioequivalence was to be concluded if the test-to-reference ratios of the 90% confidence interval of the geometric means using both the nominal and the potency corrections were contained entirely within the 0.80 to 1.25 interval for dapagliflozin and metformin AUC and $AUC_{(0-t)}$ and the geometric means of the test-to-reference ratio using both the nominal and potency correction for C_{max} was entirely within the 0.80 to 1.25 interval. If the results of this study are submitted to other regulatory authorities, bioequivalence will be concluded if the 90% confidence intervals of the test-to-reference ratios geometric means fall entirely within the 0.80 to 1.25 interval using the nominal dosage for both dapagliflozin and metformin AUC, $AUC_{(0-t)}$, and C_{max}.

Effect of food for the dapagliflozin/metformin (5 mg/850 mg) immediate-release, fixed-dose combination tablet was analysed with the same model as described above.

Changes to the planned analyses

This study was designed following the Health Canada bioequivalence guideline from 1992; however, during study implementation, the 2012 Health Canada guidelines were published. Based on these revised guidelines, the analytical plans were changed so that the potency correction was not required if the actual drug content was within 5% of the nominal. In addition, the Health Canada criteria for C_{max} only required the point estimate of the test to reference ratio to be between 80 and 125%. Since the percent label claim for all investigational product administered in this study was within 5% of the nominal, these criteria were applied to the analyses.

Subject population

Forty volunteers met the entry criteria and were enrolled in the study; 34 volunteers completed the study, 3 volunteers were withdrawn due to adverse events, 2 volunteers were withdrawn for protocol noncompliance, and 1 volunteer was withdrawn for difficult venipuncture/cannulation. All 40 volunteers were included in the safety analyses and in the pharmacokinetic analyses for those periods in which they had evaluable data.

Summary of pharmacokinetic results

Key pharmacokinetic parameters of dapagliflozin and metformin of each treatment are summarized in Table S2. Statistical comparisons of dapagliflozin and metformin key pharmacokinetic parameters of each treatment are presented in Table S3.

Table S2 Summary of key plasma pharmacokinetic parameters for dapagliflozin and metformin of each treatment

		Geometric mean (CV%)			Median (Min, Max)
Treatment	**N**	**AUC (ng*h/mL)**	**$AUC_{(0-t)}$ (ng*h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
			Dapagliflozin		
A	38	220 (27.0)	214 (26.6)	58.6 (30.4)	1.00 (0.50, 2.00)
B	36	231 (26.3)	224 (26.0)	59.7 (29.1)	1.00 (0.50, 3.00)
C	37	236 (26.0)	230 (25.6)	31.9 (34.7)	3.00 (0.50, 8.02)
D	36	243 (27.4)	235 (27.2)	37.0 (31.1)	3.00 (1.50, 8.07)
			Metformin		
A	38	9400 (26.5)[a]	9430 (27.0)	1480 (27.4)	3.00 (1.00, 5.01)
B	36	9370 (29.6)[b]	9390 (30.3)	1510 (30.4)	3.00 (1.50, 5.05)
C	37	8860 (22.9)[c]	9010 (24.4)	1140 (17.7)	4.00 (1.00, 6.02)
D	36	9140 (24.3)[d]	9130 (24.2)	1150 (20.9)	4.00 (1.50, 5.02)

[a] n = 37: Subject E0001064 had an Rsq <0.80; thus AUC was not reported for this subject.

[b] n = 35: Subject E0001064 had an Rsq <0.80; thus AUC was not reported for this subject.

[c] n = 33: Subjects E0001023, E0001035, E0001046, and E0001064 had Rsq <0.80; thus AUC values were not reported for these subjects.

[d] n = 34: Subjects E0001023 and E0001051 had Rsq <0.80; thus AUC values were not reported for these subjects.

CV% geometric coefficient of variation in percent; Max maximum; Min minimum; N number of volunteers included in pharmacokinetic analysis for that treatment and analyte; n number of values (observations).

Treatment A: Single oral doses of 5 mg dapagliflozin and 850 mg Glucophage tablets administered together in the fasted state

Treatment B: A single oral dose of dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet in the fasted state

Treatment C: Single oral doses of 5 mg dapagliflozin and 850 mg Glucophage tablets administered together in the fed state

Treatment D: A single oral dose of dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet in the fed state

Table S3 Statistical comparison of dapagliflozin and metformin key pharmacokinetic parameters of each treatment

Parameter	Treatment	n	Geometric LS mean	95% CI	Pairwise comparison		
					Pair	Ratio (%)	90% CI (%)
Dapagliflozin							
AUC (ng*h/mL)	A	38	219.7	202.0, 238.9	B/A	104.94	102.44, 107.50
	B	36	230.5	212.0, 250.7	D/C	101.11	98.68, 103.60
	C	37	238.0	218.9, 258.8	D/B	104.39	101.88, 106.95
	D	36	240.6	221.3, 261.7	C/A	108.34	105.77, 110.98
$AUC_{(0-t)}$ (ng*h/mL)	A	38	213.6	196.7, 232.1	B/A	104.85	102.31, 107.44
	B	36	224.0	206.2, 243.4	D/C	100.93	98.47, 103.45
	C	37	231.2	212.8, 251.2	D/B	104.19	101.65, 106.79
	D	36	233.4	214.8, 253.5	C/A	108.23	105.62, 110.90
C_{max} (ng/mL)	A	38	58.81	53.28, 64.91	B/A	101.45	92.14, 111.69
	B	36	59.66	53.92, 66.01	D/C	116.36	105.62, 128.20
	C	37	31.83	28.81, 35.18	D/B	62.09	56.34, 68.43
	D	36	37.04	33.49, 40.98	C/A	54.13	49.20, 59.57
Metformin							
AUC (ng*h/mL)	A	37	9499	8726, 10340	B/A	99.05	93.36, 105.08
	B	35	9409	8632, 10260	D/C	101.84	95.67, 108.42
	C	33	8997	8245, 9817	D/B	97.38	91.62, 103.50
	D	34	9162	8404, 9989	C/A	94.71	89.11, 100.66
$AUC_{(0-t)}$ (ng*h/mL)	A	38	9460	8691, 10300	B/A	98.99	93.48, 104.82
	B	36	9364	8593, 10200	D/C	101.38	95.70, 107.40
	C	37	8945	8214, 9742	D/B	96.85	91.42, 102.60
	D	36	9069	8323, 9881	C/A	94.56	89.32, 100.11
C_{max} (ng/mL)	A	38	1493	1380, 1615	B/A	101.51	95.24, 108.18
	B	36	1515	1399, 1641	D/C	101.63	95.31, 108.37
	C	37	1131	1045, 1224	D/B	75.87	71.15, 80.91
	D	36	1150	1062, 1245	C/A	75.78	71.13, 80.74

n number of values (observations).
Results based on a mixed-effects analysis of variance model (separately for each cohort) with sequence, period, and treatment as fixed effects, and volunteer nested within sequence as a random effect.
Treatment A: Single oral doses of 5 mg dapagliflozin and 850 mg Glucophage tablets administered together in the fasted state
Treatment B: A single oral dose of dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet in the fasted state

Treatment C: Single oral doses of 5 mg dapagliflozin and 850 mg Glucophage tablets administered together in the fed state
Treatment D: A single oral dose of dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet in the fed state

In the fasted state, the dapagliflozin/metformin (5 mg/850 mg) immediate-release fixed-dose combination tablet (test) was bioequivalent to the 5 mg dapagliflozin and 850 mg Glucophage tablets (reference) with respect to AUC, $AUC_{(0-t)}$, and C_{max} for both dapagliflozin and metformin (90% CIs on the geometric LS mean ratios were all within 80.00 to 125.00%).

In the fed state, the test formulation was bioequivalent to the reference with respect to AUC and $AUC_{(0-t)}$ for both dapagliflozin and metformin (90% CIs on the geometric LS mean ratios were all within 80.00 to 125.00%). C_{max} was bioequivalent for both dapagliflozin and metformin (point estimates were within 80.00 to 125.00%) based on the Canadian bioequivalence requirements but not for dapagliflozin (ratio of 116.36% and 90% CI of 105.62 to 128.20%) if requirements of other authorities were applied.

Food appeared to decrease dapagliflozin and metformin peak exposure (C_{max}) but not total exposure (AUC) in both the test and reference formulations. In the fed state, the test formulation was bioequivalent to the reference with respect to AUC and $AUC_{(0-t)}$ for both dapagliflozin and metformin (90% CIs on the geometric LS mean ratios were all within 80.00 to 125.00%) but was not bioequivalent with respect to C_{max} for dapagliflozin (ratio of 62.09% and 90% CI of 56.34 to 68.43%) and metformin (ratio of 75.87% and 90% CI of 71.15 to 80.91%). Similarly, in the fed state, the test formulation was bioequivalent to the reference with respect to AUC and $AUC_{(0-t)}$ for both dapagliflozin and metformin but was not bioequivalent with respect to C_{max} for dapagliflozin (ratio of 54.13% and 90% CI of 49.20 to 59.57%) and metformin (ratio of 75.78% and 90% CI of 71.13 to 80.74%).

In addition, median t_{max} values were generally similar between the reference and test formulations under fasted state (Treatments A and B) and under fed state (Treatments C and D) for dapagliflozin and metformin. However, median t_{max} were prolonged in the fed treatments (C and D) compared to the fasted treatments (A and B) for both analytes.

Summary of safety results

There were no deaths were reported during the study. One volunteer experienced a serious adverse event of anaemia, which was considered severe and led to study discontinuation. Two additional volunteers discontinued the study due to nonserious adverse events of haematuria and cellulitis. Apart from the adverse event of anaemia, which was of severe intensity, all adverse events were of mild or moderate intensity. All adverse events were either resolved or improving by study conclusion.

Overall, there were 26 (65.0%) volunteers with at least 1 adverse events during the study. There were fewer volunteers with events during Treatment A (7 [18.4%] volunteers) than during Treatments B (13 [36.1%] volunteers), C (12 [32.4%] volunteers), or D (12 [33.3%] volunteers). The most frequently reported adverse events overall were diarrhoea in 9 (22.5%)

volunteers and abdominal pain, catheter site related reaction, dizziness, and headache in 6 (15.0%) volunteers each.

There were no trends or clinically meaningful changes noted in mean or median clinical laboratory results or vital signs during the study; there were no relevant changes noted in electrocardiograms from screening to follow-up.