AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Dapagliflozin/metformin
Study Code	D1691C00005
Edition Number	1
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An open label, randomized, two-period, crossover study to assess the effect of food on fixed dose combination dapagliflozin/metformin tablet (5 mg/1000 mg) in healthy male and female volunteers

Study dates: First healthy volunteer enrolled: 28 June 2010
Last healthy volunteer last visit: 6 August 2010

Phase of development: Clinical pharmacology (I)

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

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**	
To assess the effect of food on the PK of dapagliflozin and metformin following the administration of the FDC tablet of dapagliflozin and metformin (5 mg/1000 mg)	Single dose C_{max}, AUC_{inf} and $AUC_{(0-t)}$	PK
	Secondary	
	Single dose t_{max} and $t_{½}$	
Secondary	**Secondary**	
To examine the safety and tolerability of the FDC tablet of dapagliflozin and metformin (5 mg/1000 mg)	Vital signs (blood pressure and heart rate), ECG, laboratory safety data (clinical chemistry, hematology and urinalysis), AEs and physical examination	Safety

AE=Adverse event, $AUC_{(0-t)}$=Area under the plasma concentration versus time curve from time zero to the time of the last measurable plasma concentration, AUC_{inf}=Total area under the plasma concentration versus time curve, C_{max}=Maximum plasma concentration, ECG=Electrocardiogram, FDC=Fixed dose combination, PK=Pharmacokinetic(s), $t_{½}$=Terminal half-life, t_{max}=Time to maximum plasma concentration following drug administration

Study design

This was a Phase I, open-label, randomized, two-period, crossover study to assess the effect of food on the PK of dapagliflozin and metformin following the administration of a single oral 5 mg dapagliflozin/1000 mg metformin FDC tablet to healthy male and female volunteers under fed and fasting conditions.

Target subject population and sample size

The target population was healthy males and healthy non-pregnant, non-lactating females who if premenopausal were using adequate birth control. The healthy volunteers were to be 18 to 55 years of age (inclusive), have a body mass index between 18 and 30 kg/m^2 (inclusive) and weigh at least 50 kg.

Up to 18 healthy volunteers were planned to be randomized aiming to obtain data from 14 completed and evaluable healthy volunteers.

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

The investigational product was an oral FDC tablet containing 5 mg dapagliflozin/1000 mg metformin manufactured by AstraZeneca AB (batchnumber: 10-001313AZ).

Duration of treatment

Each healthy volunteer received 2 single oral doses (1 in each treatment period) of the 5 mg dapagliflozin/1000 mg metformin FDC tablet. One dose was administered under fasting conditions whereas the other dose was administered following a high-fat, high-calorie meal. The washout period (days without administration of investigational product) between the 2 treatment periods was 7 to 14 days, and the expected total duration of each healthy volunteer's participation was approximately 8 weeks (from the screening visit until the follow-up visit).

Statistical methods

Pharmacokinetic and safety data were summarized using descriptive statistics.

The PK parameters AUC_{inf}, $AUC_{(0-t)}$ and C_{max} were log-transformed prior to statistical analysis. All 3 endpoints were analyzed using a mixed analysis of variance model, with sequence, period and fed/fasted state as fixed effects and subject within sequence as a random effect. The results of the analysis were presented in terms of estimated geometric means for fed and fasted states, fed/fasted effect (ratio of geometric means) and 90% confidence intervals (CIs) for the fed/fasted effect. Geometric means were estimated by back-transformation of least squares means from the log transformed data.

Subject population

In total, 24 healthy volunteers were screened (consented) and 17 healthy volunteers were randomized to treatment in the study, which was conducted at 1 center in Sweden. Eight healthy volunteers (5 males and 3 females) aged between 19 and 26 years were assigned to the fasted-fed treatment sequence, and 9 healthy volunteers (7 males and 2 females) aged between 20 and 49 years were assigned to the fed-fasted treatment sequence.

The number of healthy volunteers who completed the study was 16 (8 healthy volunteers in each treatment sequence). One healthy volunteer in the fed-fasted treatment sequence decided to discontinue from the study on Day 2 at Visit 2 after administration of 1 dose of the dapagliflozin/metformin FDC tablet in the fed state. The discontinuation was voluntary based on the healthy volunteer's own decision with no other reason provided, and he left the clinic in the evening.

All 17 randomized healthy volunteers were included in the safety analysis set, and all 16 healthy volunteers who completed the study were included in the PK analysis set.

The number of healthy volunteers and their demographic characteristics were in line with the population that was intended to be included in the study. The treatment sequences were

comparable in terms of demographics. This was according to the CSP and was considered appropriate for this Phase I study.

Summary of pharmacokinetic results

The lower limit of the 90% CI for the estimated geometric mean C_{max} fed versus fasting ratio for dapagliflozin was below 0.80 and the interval did not include 1 indicating a statistically significant difference. The point estimate was 0.71, corresponding to a decrease of 29% in C_{max} during fed conditions. The 90% CIs for the estimated geometric mean fed versus fasting ratio for AUC_{inf} and $AUC_{(0-t)}$ were both contained within the traditional bioequivalence bounds of 0.80 to 1.25 and the interval included 1, suggesting an absence of food effect.

The absorption of dapagliflozin was rapid with a median t_{max} of 1 hour (fasting), which was delayed by 1 hour during fed conditions. The geometric mean $t_{½}$ was 20.5 hours during fasting conditions and 19.0 hours during fed conditions and thus judged as comparable. The variability was low for C_{max}, AUC_{inf} and $AUC_{(0-t)}$ during both fasting and fed conditions with a CV% ranging from 23 to 30% during fasting conditions and from 20 to 22% during fed conditions. The variability for $t_{½}$ was moderate during both fasting and fed conditions with a CV% of 55% and 40%, respectively.

The lower limit of the 90% CI for the estimated geometric mean C_{max} fed versus fasting ratio for metformin was below 0.80 and the interval did not include 1 indicating a statistically significant difference. The point estimate was 0.83, corresponding to a decrease of 17% in C_{max} during fed conditions. The 90% CIs for the estimated geometric mean fed versus fasting ratio for AUC_{inf} and $AUC_{(0-t)}$ were both contained within 0.80 to 1.25 and the interval included 1, suggesting an absence of food effect.

The absorption of metformin was rapid with a median t_{max} of 2 hours (fasting), which was delayed by 2 hours during fed conditions. The geometric mean $t_{½}$ was 18.3 hours during fasting conditions and 22.3 hours during fed conditions and thus judged as comparable. The variability was low for C_{max}, AUC_{inf} and $AUC_{(0-t)}$ during both fasting and fed conditions with a CV% ranging from 16 to 31% during fasting conditions and from 13 to 21% during fed conditions. The variability for $t_{½}$ was moderate during both fasting and fed conditions with a CV% of 45% and 58%, respectively.

Summary of safety results

There were no serious AEs, discontinuations of investigational product due to AEs or other significant AEs. Approximately the same types of AEs (preferred terms) were reported after dosing with the dapagliflozin/metformin FDC tablet in the fasted and in the fed state in this open-label study, and there was no apparent difference in AE frequency between the fasting and fed conditions.

In total, 10 healthy volunteers (58.8%) receiving the dapagliflozin/metformin FDC tablet reported 18 AEs. In the fasted state, 7 healthy volunteers (43.8%) reported in total 9 AEs. Of these, 2 events of nausea were assessed by the Investigator as being causally related to treatment and to be of mild and moderate intensity, respectively. In the fed state, 7 healthy

volunteers (41.2%) reported in total 9 AEs of which 3 events (nausea, diarrhea and chills) were assessed by the Investigator as being causally related to treatment and to be of moderate or mild intensity. The laboratory samples taken for the healthy volunteer who had chills in conjunction with diarrhea were not indicative of infection. The majority (89%) of AEs were judged by the Investigator to be of mild or moderate intensity. Two of the AEs reported by 2 healthy volunteers in the fasted state were judged by the Investigator to be of severe intensity but not causally related to treatment (syncope and hordeolum of the left eyelid).

In total, the most common (defined as being reported by at least 3 healthy volunteers) AEs were nausea, headache and somnolence, which were reported by 6 healthy volunteers (35.3%), 4 healthy volunteers (23.5%) and 3 healthy volunteers (17.6%), respectively. The number of healthy volunteers with AEs was highest in the system organ classes (SOCs) Gastrointestinal disorders (n=7 [41.2%]) and Nervous system disorders (n=7 [41.2%]). In the fasted state, the most common AE was nausea, which was reported by 4 healthy volunteers (25.0%). The number of healthy volunteers with AEs was highest in the SOCs Gastrointestinal disorders (n=4 [25.0%]) and Nervous system disorders (n=4 [25.0%]). In the fed state, the most common AE was nausea, which was reported by 3 healthy volunteers (17.6%). The number of healthy volunteers with AEs was highest in the SOCs Gastrointestinal disorders (n=4 [23.5%]) and Nervous system disorders (n=4 [23.5%]).

There were no clinically relevant changes in vital signs, ECG, safety laboratory variables or physical examination during the study.