AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Dapagliflozin
Study Code	D1692C00002
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An Open-label, Multi-centre, Drug-drug Interaction Study to assess the effect of Voglibose (0.2 mg tid) on the Pharmacokinetics, Safety and Tolerability of single oral administration of dapagliflozin (10 mg) in Japanese Patients with Type 2 Diabetes

Study dates: First patient enrolled: 9 January 2010
Last patient last visit: 3 April 2010

Phase of development: Clinical pharmacology (1)

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

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Study centre(s)

2 centres were planned for participation only in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objective			Variable
Priority	**Type**	**Description**	**Description**
Primary	PK	To evaluate pharmacokinetics (PK) of dapagliflozin when administered alone or in combination with voglibose in Japanese patients with type 2 diabetes mellitus (T2DM) by assessment of AUC and C_{max} of dapagliflozin.	AUC and C_{max}
Secondary	Safety	To evaluate the safety and tolerability of dapagliflozin when administered alone or in combination with voglibose in Japanese patients with T2DM.	Adverse events (AE) Laboratory values Physical examination Electrocardiogram (ECG) Vital signs: heart rate, blood pressure
	PK	To evaluate the PK of dapagliflozin when administered alone or in combination with voglibose in Japanese patients with T2DM by assessment of AUC_{0-t}, t_{max}, $t_{1/2}$, CL/F.	AUC_{0-t}, t_{max}, $t_{1/2}$, CL/F

Study design

This was an open-label, multi-centre drug-drug interaction study to assess the effect of voglibose 0.2 mg tid on PK, safety and tolerability of dapagliflozin when a single oral dose of dapagliflozin 10 mg was administered to Japanese patients with T2DM treated with voglibose.

In this study 22 Japanese patients with T2DM were assigned to treatment. The patients were on stable treatment with voglibose at least 8 weeks before enrolment (one change in voglibose dose to 0.2 mg tid by 4 weeks before enrolment is allowed).

The study consisted of two PK sampling periods: period I of a single dose of dapagliflozin with voglibose and period II of a single dose of dapagliflozin alone. The PK sampling periods were separated by a wash-out period of 7 days between the last blood sampling in period I and the dose of dapagliflozin in period II.

In period I, each patient took a single oral dose of 10 mg dapagliflozin (Visit 2) together with voglibose and plasma samples were collected through Visit 4 (up to 72 hours = 3 days after dose) for PK assessment. In period II, after the wash-out period, a single oral dose of 10 mg dapagliflozin was administered without voglibose. Plasma samples were collected through Visit 7 (up to 72 hours = 3 days after dose) for PK assessment.

The patients took voglibose just before each meal (tid) until and including Study day 3 (Visit 4). The patients stopped taking voglibose on Study day 4 and no voglibose was taken until after the last blood sampling for PK assessment on Study day 14 (Visit 7).

Target patient population and sample size

Male or female patients with T2DM aged 20 or older.

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

Dapagliflozin 10 mg tablets. Tablets were administered orally, as a single dose in the morning during fasting conditions.

Duration of treatment

Maximum 22 days (Screening period: 7 days, Period I: 4 days, Wash-out period: 7 days, Period II: 4 days)

Statistical methods

All PK and safety data were summarised by dosing condition using descriptive statistics.

The PK variables AUC and C_{max} were log-transformed before analysis. They were analysed using a mixed model ANOVA with fixed effects for the dosing condition (with voglibose or without voglibose) and a random effect for patients. Estimates and confidence intervals of the difference between the dosing conditions were first constructed in the log scale. Then the estimates and confidence intervals of ratio of geometric means between the dosing conditions in the original scale were obtained by taking anti-logarithms. The estimates and 2-sided 90% confidence intervals of the ratio of geometric means were presented for:

- AUC (with voglibose) /AUC (without voglibose)
- C_{max} (with voglibose) / C_{max} (without voglibose)

Lack of PK drug-drug interaction was concluded if the confidence interval fell within 80% to 125% for AUC and C_{max} of dapagliflozin.

Based on Studies MB102005 and MB102026, within subject standard deviation of log (AUC) and log (C_{max}) was expected to be at most 0.095 and 0.2024, respectively. With 20 patients, the 2-sided 90% confidence intervals for ratios AUC (with voglibose) /AUC (no voglibose) and C_{max} (with voglibose) / C_{max} (no voglibose) fell within 0.8 to 1.25 with power over 99%

and 90%, respectively, if voglibose had no true effect on AUC and C_{max} of dapagliflozin. Two (10%) additional subjects were included to account for possible dropouts.

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2 of the CSP.

Patient population

The first patient was enrolled on 9 January 2010 and the last patient completed the study on 3 April 2010. A total of 28 Japanese patients with T2DM were enrolled into the study at 2 study sites and 22 of these patients were administered the investigational drug. All patients who took the investigational drug patients completed the treatment.

Seven patients had at least one protocol deviation, only one patients had a major deviation the patients took prohibited concomitant medication (Ibuprofen) during the study due to AE (gingivitis). Other 6 patients had minor deviations from the protocol-required procedure (eg, the samples of laboratory assessment were not analyzed within time-window or ECG assessments were not performed before the blood sampling). All patients were included in PK or safety analysis set.

All patients were Japanese and 13 male patients and 9 female patients were enrolled in the study. Mean of age was 52.7 and the mean of body mass index (BMI) was 26.76.

Summary of pharmacokinetic results

Estimated ratios of geometric means for AUC and C_{max} of dapagliflozin, when administered alone and in combination with voglibose, are presented in Table S2.

In Japanese patients with T2DM, the PK of dapagliflozin after a single oral dose of dapagliflozin 10 mg was not influenced by concomitant doses of voglibose (0.2 mg tid). The 2-sided 90% confidence intervals of the ratios of geometric means (dapagliflozin + voglibose / dapagliflozin) for AUC and C_{max} were well within the pre-defined interval of 0.80 to 1.25. The median t_{max} and geometric mean AUC_{0-t} and CL/F were similar between treatments and $t_{1/2}$ was not within the pre-defined target range.

Table S2 Ratio of geometric means of AUC and C_{max} between the treatments of dapagliflozin alone and in combination with voglibose (PK analysis set)

Parameter	Estimate[a]	90% CI[a]	
		Lower	Upper
AUC (Combination) / AUC (dapagliflozin)	1.009	0.954	1.067
C_{max} (Combination) / C_{max} (dapagliflozin)	1.040	0.899	1.204

Data derived from Table 11.2.3.1
Combination: dapagliflozin 10 mg qd + voglibose 0.2 mg tid
dapagliflozin : dapagliflozin 10 mg qd
a Based on ANOVA model including dosing condition as fixed effect and patients as random effect.

Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations of the investigational product due to adverse events (DAEs), or any other significant adverse event (OAEs) in the study.

Five AEs (Gingivitis, Paraesthesia oral, Oedema peripheral, Bronchitis and Pollakiuria) were reported in 5 patients (1 patient in the PK sampling period I: dapagliflozin with voglibose, 1 patient in the wash-out period and 3 patients in the PK sampling period II: dapagliflozin only). All AEs were mild or moderate intensity. No events of hypoglycaemia were reported in this study.

There were no clinically relevant treatment-related changes in any laboratory variables, vital signs, ECG and Physical examination measured in the patients exposed to dapagliflozin with or without voglibose during the study.

Dapagliflozin 10 mg was well tolerated when administered alone and in combination with voglibose 0.2 mg tid in Japanese patients with T2DM.