Drug Substance(s)	Dapagliflozin	**SYNOPSIS**	(For national authority use only)
Study Code	D1690C00001		
Date	24 October 2008		

A double-blind, randomized, four-period crossover study to assess the effects of single oral dose dapagliflozin administration on QTc interval compared to placebo, using AVELOX™ (moxifloxacin) as a positive control, in healthy male volunteers age 18 to 45 years

Study centre

Approximately 56 healthy male volunteers, aged 18 to 45 years inclusive, were to be randomised at a single centre to ensure 36 evaluable volunteers.

Study dates		**Phase of development**
First volunteer enrolled	26 July 2007	Clinical pharmacology (I)
Last volunteer completed	05 April 2008	

Objectives

The primary objective of this study was to assess the maximum of the mean changes in time-matched QTcX interval after dapagliflozin 150 mg administration compared to placebo.

The secondary objectives of this study were as follows:

1. To assess the maximum of the mean changes in time-matched QTcF, QT, and QTcB intervals after dapagliflozin 150 mg administration compared to placebo

2. To assess the maximum of the mean changes in time-matched QTcX, QTcF, QT, QTcB intervals after moxifloxacin 400 mg administration compared to placebo

3. To assess the maximum of the mean changes in time-matched QTcX, QTcF, QT, and QTcB intervals after dapagliflozin 20 mg administration compared to placebo

4. To assess the pharmacokinetics of dapagliflozin 150 mg, 20 mg, and its metabolite, BMS-801576, in healthy male volunteers

5. To explore the relationship between plasma concentration and the cardiac ventricular repolarisation effect on the heart during the first 24 hours after a single oral dose of dapagliflozin in healthy volunteers by assessments of plasma concentrations of dapagliflozin and its metabolite, BMS-801576, and digital electrocardiograms (dECG)

6. To examine the safety and tolerability of dapagliflozin by assessment of adverse events (AE), laboratory variables, electrocardiograms and vital signs

Study design

This was a single-centre, randomised, double-blind, double-dummy, placebo-controlled, crossover study involving 4 single-dose treatment periods. There was a 7 to 10 days washout period between each period.

Target volunteer population and sample size

Approximately 56 healthy male volunteers aged 18 to 45 years, inclusive, were to be randomised at a single centre to ensure 36 evaluable volunteers.

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

The following investigational products were used:

- Dapagliflozin 150 mg (3 x 50 mg tablets) (batch numbers: H 1950-01-01-01, 5H06032), oral administration
- Placebo to dapagliflozin tablet (batch numbers: H 1952-01-01-01, 5L02123), oral administration
- Dapagliflozin 20 mg (2 x 10 mg capsules) (batch numbers: H 1948-01-01-01, 3L67394), oral administration
- Placebo to dapagliflozin capsule (batch numbers: H 1949-01-01-01, 4J87417), oral administration
- Over-encapsulated moxifloxacin capsule 400 mg (batch numbers: H 1790-02-01-01, 7A28405), oral administration
- Placebo to over-encapsulated moxifloxacin capsule (batch numbers: H 1951-01-01-01, 6L19129), oral administration

Each healthy volunteer was to receive all of the following treatment regimens according to a randomised dose sequence:

- **Treatment A:** 150 mg dapagliflozin (3 x 50 mg tablets) plus dapagliflozin placebo (2 capsules) plus moxifloxacin placebo (1 capsule)

- **Treatment B:** dapagliflozin placebo (3 tablets) plus 20 mg dapagliflozin (2 x 10 mg capsules) plus moxifloxacin placebo (1 capsule)

- **Treatment C:** dapagliflozin placebo (3 tablets) plus dapagliflozin placebo (2 capsules) plus over-encapsulated moxifloxacin (1 x 400 mg capsule)

- **Treatment D:** dapagliflozin placebo (3 tablets) plus dapagliflozin placebo (2 capsules) plus moxifloxacin placebo (1 capsule)

Duration of treatment

The duration of healthy volunteer participation was approximately 65 days.

Variables

Pharmacokinetic

- Secondary: Maximum plasma drug concentration after single-dose administration (C_{max}), time to reach maximum drug concentration or maximum response following drug administration (t_{max}), area under the plasma concentration-time curve from time 0 to infinity (AUC), area under the plasma concentration-time curve from time 0 to time t ($AUC_{(0-t)}$), area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{(0-24)}$); half-life ($t_{½}$)

Pharmacodynamic

- Primary: The time interval of ventricular depolarisation and repolarisation (QT) interval corrected for heart rate using a study-specific factor (QTcX)

- Secondary: the QT interval corrected for heart rate using the Fridericia correction (QTcF) and the QT interval corrected for heart rate using the Bazett formula (QTcB)

Safety

- Secondary: frequency and severity of AEs and results of clinical laboratory tests, vital signs testing, safety ECGs, and physical examinations.

Statistical methods

Statistical analysis was conducted on corrected QT intervals measured from lead V_2 as the primary analysed lead, with lead V_5 as the backup lead when lead V_2 was found to be unsuitable for analysis or evaluation. Before statistical analyses was performed, the ECG intervals were smoothed on an individual basis.

Analysis for QTcX was done according to the following procedures: 3 different contrasts (dapagliflozin 150 mg versus placebo, dapagliflozin 20 mg versus placebo and moxifloxacin versus placebo) were estimated in the same model. Each subject contributed 4 sets of QTcX measurements, 1 for each period. The smoothed intervals of QTcX at time points 0.5, 1, 2, 3, and 4 hours and 6, 8, 12, and 24 hours were then analysed by repeated measures analysis of covariance models with the independent factors of subject, treatment, period, time (ie, time of ECG sampling from which QTc was measured relative to dosing at time 0 hour), the interaction of period and time, the interaction of treatment and time, and baseline QTcX value as a covariate. Volunteer within sequence was treated as a random effect. An autoregression of the first order correlation structure was assumed to describe the relationship between the response variables. The treatment effect was estimated together with its 2-sided 90% confidence interval (CI) at each of the 9 time points. To test the treatment effect of dapagliflozin, the upper bounds of all 2-sided 90% CIs were evaluated against the margin of 10 ms. To test the treatment effect of moxifloxacin, the average of baseline-adjusted QTcX values from 1, 2, 3, and 4 hours was derived relative to placebo, and the lower bound of the corresponding 90% CI was evaluated against the margin of 5 ms. The smoothed intervals of QTcF and QTcB were also analysed in the same repeated-measures ANCOVA model, at the same time points.

A plasma concentration to QT (C-QT) analysis was presented using a linear mixed model in which the placebo-subtracted change from baseline in QTcX was the dependent variable and the plasma concentration from all doses of dapagliflozin was the independent variable. The intersection and plasma concentration were treated as random effect. The null hypothesis of zero-slope was tested with a 2-sided t-test at the 10% significance level.

Volunteer population

A total of 50 volunteers from a single centre were enrolled (ie, gave informed consent), randomised to a treatment sequence, and received study drug. The first volunteer signed informed consent for the study on 26 July 2007, and the last volunteer completed the study on 05 April 2008. Thirteen volunteers were discontinued from the study. Of these, 6 (12.0%) volunteers were discontinued because they were unwilling to continue, 3 (6.0%) for severe noncompliance with the protocol requirements, 2 (4.0%) for safety reasons, 1 (2.0%) due to AEs (headache, myalgia, and pharyngolaryngeal pain), and 1 (2.0%) due to other reason. The study population consisted of males between the ages of 19 and 44 years; the mean age was 31.7 years. No volunteers were taking any medications prior to entering this study, and 3 (6%) volunteers received concomitant medication.

Summary of pharmacokinetic results

Dapagliflozin was rapidly absorbed after administration of a single oral dose of 150 or 20 mg, with the medians of the maximum plasma concentrations occurring at 1 hour after administration. The geometric mean C_{max} and AUC values appeared to increase in a dose proportional manner. The geometric mean $t_{½}$ value was 14.8 hours after dapagliflozin 150 mg administration and 13.8 hours after dapagliflozin 20 mg administration.

The medians of the maximum plasma concentrations of the dapagliflozin metabolite BMS-801576 were reached at 2 hours after administration of dapagliflozin 150 or 20 mg. The geometric mean C_{max} and AUC values for the metabolite BMS-801576 appeared to increase in a dose proportional manner. The geometric mean $t_{½}$ value for the metabolite was 14.0 hours after dapagliflozin 150 mg administration and 12.4 hours after dapagliflozin 20 mg administration.

Summary of pharmacodynamic results

QTcX

The maximum of the placebo-corrected, baseline-adjusted, mean effect of dapagliflozin 150 mg for QTcX was 1.2 ms at 3 hours post dose, and the upper bound of the 2-sided 90% CI was 3.4 ms. For dapagliflozin 20 mg, the maximum of the placebo-corrected, baseline adjusted mean effect for QTcX was 2.3 ms at 8 hours post dose, and the upper bound of the 2-sided 90% CI was 4.6 ms.

Figure S 1 shows the placebo-corrected, baseline adjusted, LS mean difference in QTcX vs. sample time by treatment.

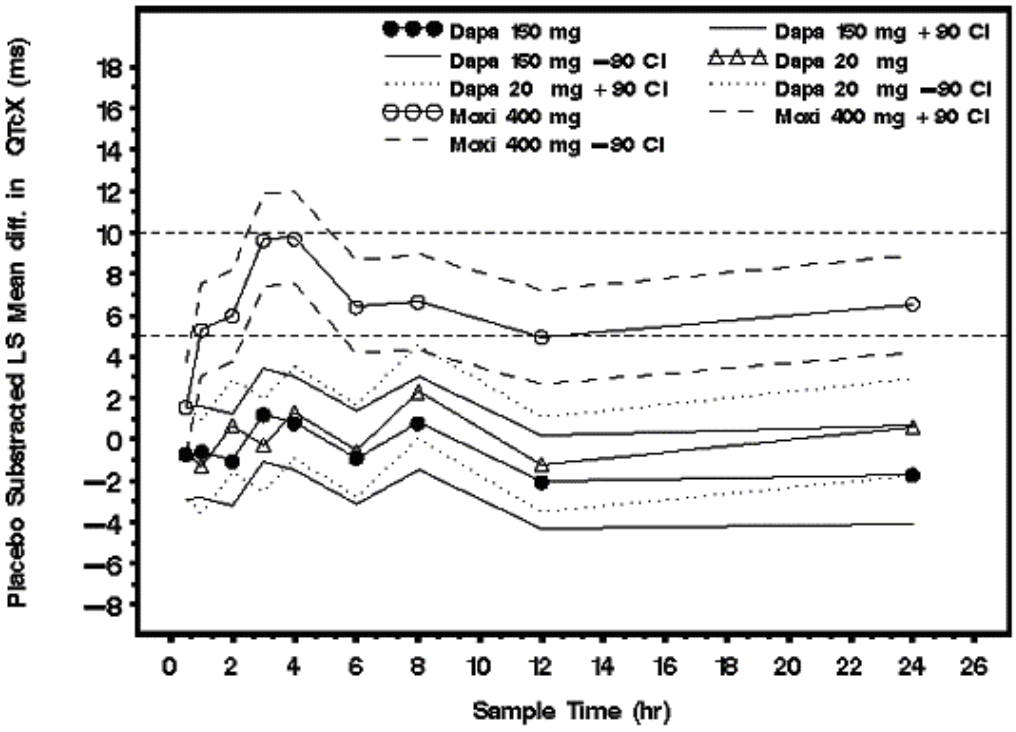
The maximum placebo-corrected, baseline-adjusted mean effect of moxifloxacin for QTcX was 9.7 ms at 4 hours post dose, and the lower bound of the 2-sided 90% CI was 7.5 ms. A predefined assay sensitivity analysis constructed from the average QTcX of moxifloxacin and placebo from hours 1 to 4 gave an increase of placebo-corrected, baseline-adjusted QTcX effect of 7.7 ms with a lower bound of the 90% CI of 6.2 ms. As this lower bound was greater than 5 ms, assay sensitivity was demonstrated.

No volunteer had a smoothed QTcX value that >450 ms during the study. There was no increase from baseline >30 ms for QTcX over the 24-hour period after dapagliflozin (150 or 20 mg) administration.

QTcF

The maximum of the placebo-corrected, baseline-adjusted, mean effect of dapagliflozin 150 mg for QTcF was 1.6 ms at 8 hours post dose, and the upper bound of the 2-sided 90% CI was 3.9 ms. For dapagliflozin 20 mg, the maximum of the placebo-corrected, baseline- adjusted mean effect for QTcF was 2.8 ms at 8 hours post dose, and the upper bound of the 2-sided 90% CI was 5.1 ms.

Figure S 1 Placebo-corrected, baseline-adjusted, LS mean difference in QTcX vs. sample time by treatment (PD analysis set)



Dapa Dapagliflozin; PD Pharmacodynamic; QTcX QT interval corrected for heart rate using a study-specific factor; LS Least squares.

Summary of pharmacokinetic/pharmacodynamic correlations

The C-QT model demonstrated a relatively flat relationship between the plasma concentration of dapagliflozin and the placebo-corrected QTcX change from baseline.

Visual inspection showed that the relationship between dapagliflozin (150 and 20 mg) or BMS-801576 plasma concentrations and changes in QTcX was relatively flat. Similar results were observed for dapagliflozin (150 and 20 mg) or BMS-801576 plasma concentrations and changes in QTcF or QTcB.

Summary of safety results

A total of 19 volunteers had AEs during the study, including 9 volunteers who had AEs after dapagliflozin administration. With the exception of Volunteer E0001134, there was a unique set of volunteers with AEs during each of the 4 treatment periods. Volunteer E0001134 had different AEs after administration of the 2 doses of dapagliflozin. Headache was the only AE that was reported in more than 1 volunteer after dapagliflozin administration, occurring in 3 volunteers who received the 150-mg dose, and 2 volunteers who received the 20-mg dose. There were no deaths, serious adverse events (SAE), or other significant adverse events

(OAE) with dapagliflozin treatment, with 1 volunteer discontinuing due to AEs (headache, myalgia, and pharyngolaryngeal pain) occurring after dapagliflozin 150 mg administration. There were no clinically significant changes in laboratory parameters for haematology or clinical chemistry. The most notable finding on urinalysis was positive glucose on Day 3 in the majority of volunteers after dapagliflozin administration (43/44, 97.7% for 150 mg and 35/40, 87.5% for dapagliflozin 20 mg). This finding is consistent with the mechanism of action of a drug that lowers plasma glucose by inhibiting the renal reabsorption of glucose and promoting its urinary excretion. No clinically significant changes were evident in results of vital signs testing, safety ECG monitoring, or physical examination findings for any volunteer following dapagliflozin administration.