Clinical Study Report	
Drug Substance	Dapagliflozin/Metformin XR FDC
Study Code	D1691C00011
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A Single-centre, Parallel-cohort, Randomized, Open-label, Two-period, Cross-over, Bioequivalence Study of the Fixed Dose Combination of Dapagliflozin/Metformin XR Relative to Co-administration of the Individual Components in Two Cohorts of Healthy Chinese Subjects in the Fed State

Study dates: First subject enrolled: 12 April 2021
Last subject last visit: 15 June 2021
The analyses presented in this report are based on a database lock date of 31 August 2021

Phase of development: Phase I (Bioequivalence)

Principal Investigator: [redacted]
China

Sponsor's Responsible Medical Officer: [redacted]
United States

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

Study centre(s)

This study was a single center study in China.

The Principal Investigator was [redacted] at [redacted] China [redacted]

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	PK	To assess the pharmacokinetic parameters of dapagliflozin and metformin in healthy Chinese subjects in the fed state: To demonstrate bioequivalence in the dapagliflozin and metformin plasma concentrations of 5 mg dapagliflozin/500 mg metformin XR FDC tablet with co-administration of a 5 mg dapagliflozin tablet and a 500 mg metformin XR (Glucophage XR®) tablets. To demonstrate bioequivalence in the dapagliflozin and metformin plasma concentrations of 10mg dapagliflozin/1000 mg metformin XR FDC tablet with co-administration of a 10 mg dapagliflozin tablet and two 500 mg metformin XR (Glucophage XR®) tablets.	Plasma AUCinf, AUClast and Cmax of dapagliflozin and metformin respectively.
Secondary	PK	To characterise the pharmacokinetic profiles of dapagliflozin and metformin when administered as the two formulations (fixed dose combination and free combination) in the fed state.	Plasma tmax, λz, t½λz, CL/F and Vz/F of dapagliflozin and metformin.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Safety	To further assess the safety and tolerability of dapagliflozin/metformin XR FDC and co-administration of the individual components in healthy Chinese subjects in the fed state.	Adverse events, vital signs, physical examination, 12-lead ECGs, clinical chemistry, haematology and urinalysis laboratory tests.

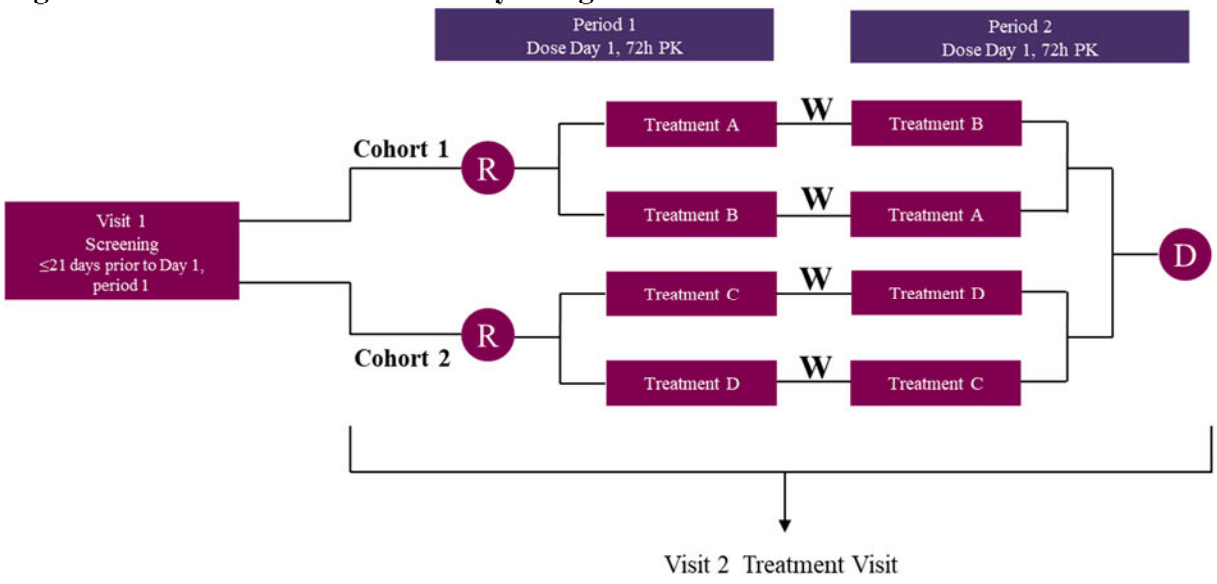
Study design

This study was a single-centre, parallel-cohort, randomized, open-label, 2-period, cross-over study in healthy Chinese subjects in fed state. The study design schematic is presented in Figure S1.

There were two independent cohorts of healthy volunteers who each received two treatments in a randomized order, and each treatment was followed by 72 hours of blood sampling for pharmacokinetic assessments, with safety and tolerability.

Healthy volunteers underwent screening evaluations to determine eligibility within 21 days prior to first dose of IP. In each cohort, approximately 40 healthy volunteers were randomized to receive treatment with IP in order to complete at least 36 evaluable subjects. Healthy volunteers were resident from prior to the evening meal the night before dosing (Day-1 of Period 1) until at least 72 hours after their last dose of IP (Day 4 of Period 2). There was a minimum of 7 days and maximum of 14 days washout between the doses given.

Figure S1 Flow Chart of Study Design



R = Randomization (Day -1, Period 1)
D = Discharge (Day 4, Period 2)
W = Washout (≥7 days and ≤14 days between doses given on Day 1 of each period)
Treatment A = Co-administration of a single oral dose of a 5mg dapagliflozin tablet and a 500mg metformin XR (Glucophage XR®) tablet
Treatment B = Single FDC tablet consisting of 5mg dapagliflozin and 500mg metformin XR
Treatment C = Co-administration of a single oral dose of a 10mg dapagliflozin tablet and two 500mg metformin XR (Glucophage XR®) tablets
Treatment D = Single FDC tablet consisting of 10mg dapagliflozin and 1000mg metformin XR

Target subject population

Healthy (as determined by no clinically significant deviation from normal in medical history, physical examination, vital signs, 12-lead ECGs, and clinical laboratory evaluations) Chinese men and women, ages 18 to 55 years, inclusive, weight at least 50 kg (for male) and 45 kg (for female), respectively, and BMI ≥19 and <26 kg/m2, were eligible to participate in the study.

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

The IP was supplied by AstraZeneca and Merck Serono.

Details of the IP are given in the following table.

Investigational product	Dosage form and strength	Manufacturer	Manufacturing Lot Numbers:
Dapagliflozin/metformin hydrochloride XR 5mg/500mg	Extended Release film coated tablets 5mg/500mg	AstraZeneca	28477.2/1

Investigational product	Dosage form and strength	Manufacturer	Manufacturing Lot Numbers:
Dapagliflozin/metformin hydrochloride XR 10mg/1000mg	Extended Release film coated tablets 10mg/1000mg	AstraZeneca	28477.1/1
Forxiga® 5mg - Dapagliflozin	Film coated tablets 5mg	AstraZeneca	28477.3/1
Forxiga® 10mg - Dapagliflozin	Film coated tablets 10mg	AstraZeneca	28477.4/1
Glucophage XR® 500mg -Metformin hydrochloride XR	Extended Release film coated tablets 500mg	Merck Serono	28477.5/1

Duration of treatment

The maximum duration is 39 days, including an up to 21 days screening period, and a minimum of 11 days and maximum of 18 days treatment period.

Statistical methods

Sample size determination:

40 healthy volunteers for each cohort (80 healthy volunteers in total) were planned to be randomized.

For each cohort, if there was no difference between the bioavailability of dapagliflozin following administration of the FDC and IC tablets under the fed condition, then 36 healthy volunteers would provide 96%, and 99% power to conclude bioequivalence with respect to Cmax and AUCinf, respectively. If there is a 5% difference, then 36 healthy volunteers would provide 89% and 99% power to conclude bioequivalence with respect to Cmax and AUCinf, respectively. If there was no difference between the bioavailability of metformin following administration of FDC tablets and IC tablets, then 36 healthy volunteers would provide 98% and 99% power to conclude bioequivalence with respect to Cmax and AUCinf, respectively. If there is a 5% difference, then 36 healthy volunteers would provide 93% and 99% power to conclude bioequivalence with respect to Cmax and AUCinf, respectively.

The above calculations for dapagliflozin assume that Cmax and AUCinf of dapagliflozin were log-normally distributed with intra-healthy volunteer standard deviations (SDs) of log (Cmax) and log (AUCinf) no greater than 0.25 and 0.1, respectively. The calculations for metformin also assumed that the Cmax and AUCinf of metformin were log-normally distributed with intra-healthy volunteer SDs of log (Cmax) and log (AUCinf) no greater than 0.23 and 0.18, respectively.

All the power calculations were performed in nQuery + nTerim 3.0. To allow for dropouts and no evaluable PK parameters in some healthy volunteers, 40 healthy volunteers for each cohort (80 healthy volunteers in total) would be randomized.

Pharmacokinetics

Bioequivalence was determined separately for dapagliflozin and metformin between Treatment A (reference) and B (test), and between Treatment C (reference) and D (test), respectively.

Bioequivalence was determined separately for each cohort using two one-sided tests. If the 90% CIs for Treatment B to Treatment A ratios of geometric means for AUCinf, AUClast and Cmax (when expressed as a percentage) are entirely contained within 80% and 125%, it would be concluded that the 2 formulations are bioequivalent. The same determination was made for Treatment C and Treatment D.

Analyses were performed by fitting a separate general linear mixed model for each PK parameter with natural logarithm of AUCinf, AUClast and Cmax as the response variables, sequence, period and treatment as fixed effects, and subject nested within sequence as random effects using bioequivalence analysis set. Separate models were fit to each parameter for each cohort. Least square mean estimates were transformed back from the logarithmic scale by exponentiation, geometric means together with confidence intervals (CIs) (2-sided 95%) for AUCinf, AUClast and Cmax were estimated and presented. To estimate the within-subject variance, CV% is defined as ((exp(variance) - 1) ^ 0.5) × 100, where the residual variance term was taken from the associated linear model.

The least square mean difference (test - reference) and the corresponding 90% CI were estimated on the natural logarithmic scale and converted back to the arithmetic scale for AUCinf, AUClast and Cmax. The resultant geometric ratio (test/reference) was used to compare treatment groups. Ratios of geometric means and the corresponding CIs (2-sided 90%) were derived and presented.

Safety

All safety variables were summarized using the safety analysis set. AEs including SAEs experienced by any subject at any time during the entire study were coded using the MedDRA version 24.0.

For each cohort, treatment emergent adverse events (TEAEs) were presented for each treatment group and overall by SOC and PT covering number and percentage of healthy volunteers reporting at least one event (ie, multiple occurrences of an TEAE for a healthy volunteer were only counted once).

All continuous laboratory variables, vital signs variables (pulse rate, systolic blood pressure, diastolic blood pressure, body temperature, weight and respiratory rate), and 12-lead ECGs were summarized by absolute values at each analysis visit by treatment group, together with the corresponding changes from baseline.

Subject population

Forty healthy volunteers were assigned to each cohort and a total of 80 healthy volunteers were randomised into the study.

All randomised healthy volunteers (100%) in cohort 1 received the study treatment, 39 healthy volunteers completed the study and 1 subject withdrew from the study due to AE.

In cohort 2, 39 (97.5%) healthy volunteers received the study treatment and completed the study, 1 healthy volunteer withdrew from the study for not taking the low-fat meal and did not receive treatment.

Summary of pharmacokinetic results

Between the FDC tablet of dapagliflozin/metformin and co-administration of the ICs (5/500 mg and 10/1000 mg, respectively) in the fed state, the 90% CIs of exposure parameters (Cmax, AUClast and AUCinf) lie entirely within the 80%-125% limits, establishing BE of both dapagliflozin and metformin.

Pharmacokinetic profiles of dapagliflozin/metformin were characterized when administered as FDC and ICs at doses of 5/500 mg and 10/1000 mg. The mean plasma concentration-time profiles of dapagliflozin/metformin were superimposable and the derived PK parameters were similar between the two formulations.

Summary of safety results

Most (78/80) of the subjects received 100% of their planned dose; 1 subject in cohort 1 withdrew from the study due to AE during treatment A (co-administration dapagliflozin 5 mg and metformin XR 500 mg) and did not take treatment B (FDC dapagliflozin/metformin XR 5/500 mg); 1 subject in cohort 2 withdrew from the study for not taking the 100% low-fat meal within prescribed time and did not receive any treatment.

In total, 18 (45.0%) subjects in cohort 1 and 17 (43.6%) subjects in cohort 2 reported at least 1 TEAE. Half of the total TEAEs reported (13/26) in cohort 1 and more than half of the total TEAEs reported (21/28) in cohort 2 are in the investigation SOC. All TEAEs except 1 were considered to be related to the IP. All TEAEs were mild in intensity.

No deaths or SAEs were reported in this study. One subject in cohort 1 reported 1 TEAE (liver injury) leading to dose discontinuation after receiving co-administration of dapagliflozin 5mg and metformin XR 500mg.

No clinically meaningful results were identified for vital signs, ECGs, or for laboratory variables.

Conclusion(s)

- Bioequivalence of both dapagliflozin and metformin were established between the FDC tablet of dapagliflozin /metformin and co-administration of the IC tablets in the fed state (5/500 mg and 10/1000 mg, respectively).
- The FDC tablets of dapagliflozin /metformin and co-administration of the IC tablets (5/500 mg and 10/1000 mg) were well tolerated in Chinese healthy volunteers in the fed states. No new safety findings were observed during the study.