AstraZeneca

**Clinical Study Report Synopsis**

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|---|---|
| Drug Substance | Dapagliflozin |
| Study Code | D1691C00004 |
| Edition Number | 1 |
| Date | 24 August 2010 |

# An open-label, randomised, two-period crossover study to assess the effect of dapagliflozin on percent inhibition of glucose re-absorption when administered once a day (10 mg OD) versus twice a day (5 mg BID) in healthy male and female volunteers

**Study dates:** First healthy volunteer enrolled: 10 February 2010
Last healthy volunteer completed: 19 April 2010

**Phase of development:** Clinical pharmacology (I)

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

## Study centre

Early Phase Clinical Unit – Berlin, PAREXEL International GmbH, Berlin, Germany.

## 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 dapagliflozin on % inhibition of glucose re-absorption (IRGRA[%]) when dapagliflozin is administered once a day (10 mg) versus twice a day (5 mg every 12 hours) at steady-state (after 5 days of dosing). | IRGRA(%) over 24 hours; based on the amount of glucose in urine, the glomerular filtration rate (GFR) and the mean serum glucose concentration (MSGC). | PD |
| **Secondary** | **Secondary** | |
| To assess the effect of dapagliflozin on urine glucose excretion when administered once a day (10 mg) versus twice a day (5 mg every12 hours) at steady-state (after 5 days of dosing). | Total urinary glucose excretion over 24 hours ($Ugluc_{24h}$);<br>amount of creatinine in urine. | PD |
| To examine the safety and tolerability of dapagliflozin dosed once a day versus twice a day. | AEs; safety laboratory variables (haematology, clinical chemistry, urinalysis); resting 12-lead ECG; vital signs; oral body temperature; body weight; physical examination. | Safety |
| To determine the PK parameters for dapagliflozin dosed twice a day versus once a day at steady-state. | $AUC_{(0\text{-}12,\ day\ 1)}$; $AUC_{(0\text{-}24,\ day\ 1)}$; $AUC_{ss,(0\text{-}12)}$; $AUC_{ss,(12\text{-}24)}$; $AUC_{ss,(0\text{-}24)}$; $AUC_{ss,(t\text{-}t+4)}$; $C_{ss,av}$; $C_{ss,av,t\text{-}t+4}$; $C_{max}$; $C_{ss,max}$; $C_{ss,min}$;<br>$t_{ss,max}$; $R_{ac(AUC)}$; $R_{ac(Cmax)}$; $DF\% = (C_{ss,\ max} - C_{ss,\ min})/C_{ss,av}$ x100%. | PK |
| **Exploratory** | **Exploratory** | |
| To indirectly determine if dapagliflozin may inhibit the rate of gut glucose absorption by comparing the plasma glucose, insulin, and GIP (glucose-dependent insulinotropic polypeptide) responses to meals accompanied with once or twice daily administration of dapagliflozin. | Baseline adjusted glucose $AUE_{0\text{-}180}$ after breakfast, lunch and dinner;<br>baseline adjusted insulin $AUE_{0\text{-}180}$ after breakfast, lunch and dinner;<br>change in GIP plasma concentration before and after dinner. | PD |
| To explore plasma concentration versus urine glucose excretion relationship. | | PK/PD |

## Study design

This was an open-label, randomised, two-period crossover, single-centre study to assess the effect of dapagliflozin dosed once a day versus twice a day. The doses of dapagliflozin were 10 mg for once daily dosing and 5 mg every 12 hours for twice daily dosing. Each dose was administered for 5 days, with a 7 to 10 days wash-out between. Sixteen healthy volunteers were enrolled (females of non-childbearing potential or being abstinent and males) to obtain 14 completed and evaluable healthy volunteers.

## Target subject population and sample size

Healthy male and female volunteers aged 18 to 45 years both inclusive. Female subjects were to be non-fertile or were to be abstinent during the study.

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

- Dapagliflozin tablets 5 mg, orally administered every 12 hours for 5 days (total daily dose 10 mg); batch number: 08–002213AZ.

- Dapagliflozin tablets 10 mg, orally administered as once daily dose for 5 days; batch number: 08-003394AZ.

## Duration of treatment

Each healthy volunteer received each treatment for 5 days, both treatment periods were separated by 7 to 10 days. Total duration of the experimental part was 17 to 20 days.

## Statistical methods

The primary objective of this study was to assess the effect of twice-daily dosing versus once-daily dosing of the same total daily dose of dapagliflozin on % inhibition of renal glucose re-absorption (IRGRA[%]). Given that the goal was one of estimation rather than hypothesis testing, no power calculation had been performed.

The primary PD endpoint IRGRA(%) over 24 hours, secondary PD endpoint $Ugluc_{24h}$, and the PK parameters $AUC_{ss,0-24}$, $C_{ss,max}$ $C_{ss,min}$ and $C_{ss,av}$ were analysed using an analysis of variance (ANOVA) model, with sequence, period and treatment (5 mg dapagliflozin every 12 hours x 5 days versus 10 mg dapagliflozin once a day x 5 days) as fixed effects and subject within sequence as a random effect. Least square means and differences in least square means of these variables together with corresponding confidence intervals (CIs) were back-transformed to provide estimates of geometric means with 95% CIs and the ratio of geometric means with 90% CIs , following adjustment for other factors in the model.

A non-parametric analysis of the treatment regimen differences for RGRA was performed using the Hodges-Lehmann estimator of the median difference together with a corresponding exact 95% CI based on the assumptions that one or more of the ANOVA model assumptions were not valid.

For plasma glucose and insulin the $AUE_{(0-180)}$ after each meal was derived and analysed using an analysis of co-variance (ANCOVA) model with sequence, period and treatment as fixed effects, subject within sequence as a random effect and baseline concentration as continuous covariate. $AUE_{(0-180)}$ after each meal was analysed in separate models and were log-transformed prior to analysis. Least square means and differences in least square means together with corresponding CIs were back-transformed to provide estimates of baseline adjusted between both treatments, which were estimated by a linear model on the log-transformed AUEs after each meal and retransformation of the point estimates and 95% CIs and the ratio of geometric means with 90%CIs, following adjustment for other factors in the model.

The absolute differences between the two GIP samples (pre- and post-dinner) were compared between treatments by applying an ANOVA model with treatment, sequence and period as fixed effects and subjects nested within sequence as random effect. The GIP differences were log-transformed prior to analysis. Least square means and differences in least square means together with corresponding CIs were back-transformed to provide estimates of geometric means with 95% CIs and the ratio of geometric means with 90% CIs, following adjustment for other factors in the model.

The absolute difference between the two GIP samples was also compared between periods for each subject by a paired t-test. Since the data indicated being not normally distributed, a Wilcoxon signed-rank test was also used.

The relationship of dapagliflozin plasma concentration versus IRGRA(%) or urine glucose excretion was explored.

**Sample Size Calculation**

If 14 subjects completed both periods of the study and if the intra-subject variance was one half the total variance observed in the 10 mg group on Day 7 for average percent inhibition of glucose re-absorption over 0-12 hours in Bristol-Myers Squibb Study MB102002 ($mean/SD_{total}$=24.5%/15.4%), then a 95% confidence interval for the difference between regimens in mean percent inhibition of glucose re-absorption over 24 hours ($\delta$) was expected to be approximately $\delta \pm 9.0$ percentage points.

**Subject population**

In total, 16 healthy male and non-fertile female subjects were randomised into the study. Eight subjects each were allocated to one of the 2 treatment sequences (AB and BA) to receive both IPs each over 5 days. All subjects completed this study in accordance with the Clinical Study Protocol. No subject was prematurely discontinued.

The PD, PK and safety analysis sets each included all 16 randomised subjects.

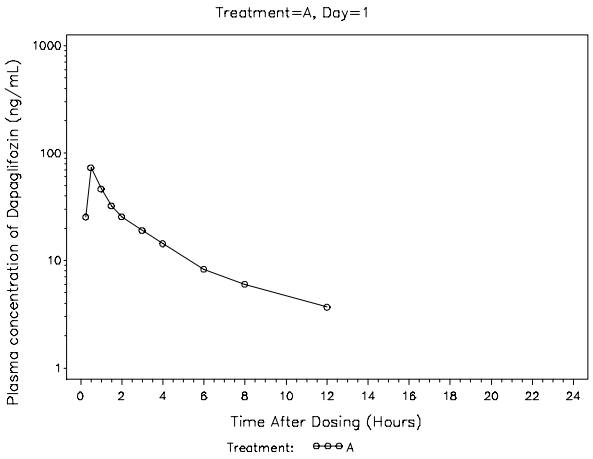
Overall, the treatment groups were well balanced with regards to demographic and baseline characteristics.

## Summary of pharmacokinetic results

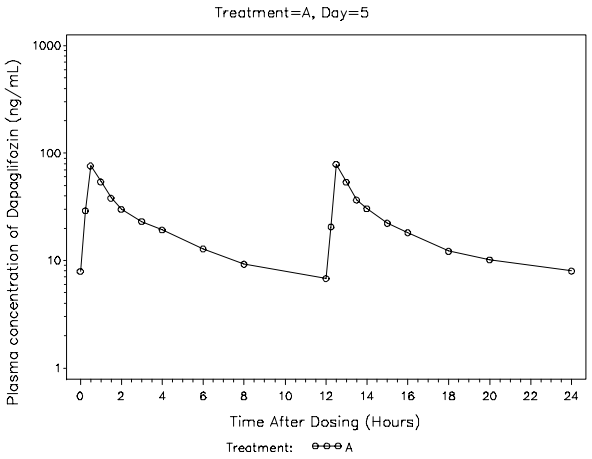
The geometric mean plasma concentration-time profiles of dapagliflozin in linear-log scale following single (Day 1) and multiple (Day 5) dose administration of dapagliflozin 5 mg every 12 hours and 10 mg once a day are shown in Figure S1.

**Figure S1 Geometric mean dapagliflozin plasma concentrations (ng/mL) over time, linear-log scale – PK analysis set**

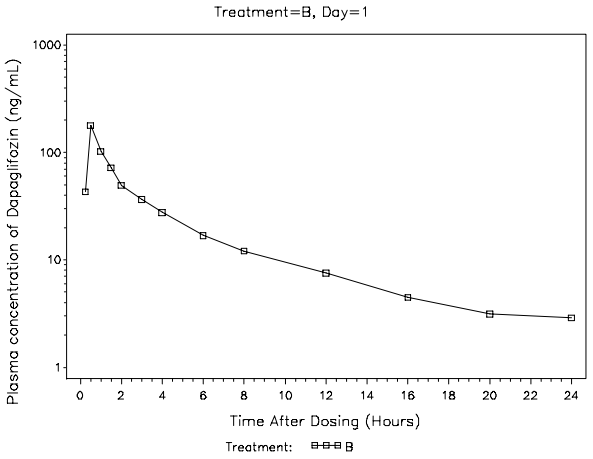
**Dapagliflozin 5 mg every 12 hours, Day 1**



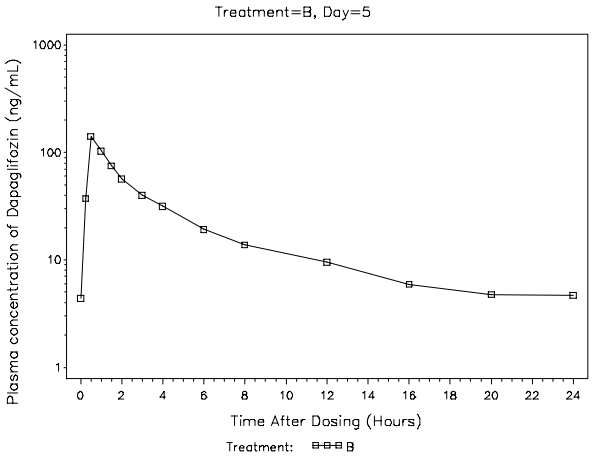

**Dapagliflozin 5 mg every 12 hours, Day 5**




**Dapagliflozin 10 mg once a day, Day 1**




**Dapagliflozin 10 mg once a day, Day 5**




Treatment A - 5 mg dapagliflozin administered every 12 hours for 5 days;
Treatment B - 10 mg dapagliflozin administered once a day for 5 days.

**Table S2 Summary of pharmacokinetic parameters of dapagliflozin – PK analysis set**

| Trt./Day | Parameter | | N | Amean | SD | Gmean | CV (%) | Min | Median | Max |
|---|---|---|---|---|---|---|---|---|---|---|
| **A (Dapagliflozin 5 mg every 12 hours)** | | | | | | | | | | |
| **Day 1** | $C_{max}$ | (ng/mL) | 16 | 82.1 | 40.0 | 73.5 | 52.2 | 30.9 | 64.8 | 174 |
| | $AUC_{(0\text{-}12,\ day\ 1)}$ | (ng*h/mL) | 16 | 186.0 | 53.5 | 178 | 33.0 | 87.2 | 196 | 295 |
| **Day 5** | $C_{ss,max}$ | (ng/mL) | 16 | 84.7 | 31.1 | 79.6 | 37.3 | 48.9 | 71.0 | 143 |
| | $t_{ss,max}$ | (h) | 16 | – | – | – | – | 0.500 | 0.500 | 1.00 |
| | $C_{ss,min}$ | (ng/mL) | 16 | 7.15 | 2.46 | 6.76 | 36.5 | 2.99 | 7.56 | 13.5 |
| | $C_{ss,av}$ | (ng/mL) | 16 | 19.5 | 4.96 | 18.8 | 28.9 | 9.59 | 20.5 | 29.1 |
| | **DF** | (%) | 16 | 405 | 126 | 383 | 38.5 | 171 | 432 | 588 |
| | $R_{ac(Cmax)}$ | | 16 | 1.14 | 0.380 | 1.08 | 33.2 | 0.597 | 1.10 | 2.09 |
| | $R_{ac(AUC)}$ | | 16 | 1.28 | 0.150 | 1.27 | 11.5 | 1.04 | 1.25 | 1.62 |
| | $AUC_{ss,(0\text{-}12)}$ | (ng*h/mL) | 16 | 240 | 61.6 | 232 | 28.9 | 119 | 243 | 337 |
| | $AUC_{ss,(12\text{-}24)}$ | (ng*h/mL) | 16 | 234 | 59.5 | 226 | 28.9 | 115 | 246 | 349 |
| | $AUC_{ss,(0\text{-}24)}$ | (ng*h/mL) | 16 | 474 | 120 | 458 | 28.7 | 234 | 494 | 681 |
| **B (Dapagliflozin 10 mg once a day)** | | | | | | | | | | |
| **Day 1** | $C_{max}$ | (ng/mL) | 16 | 190 | 64 | 179 | 37.8 | 86.4 | 193 | 312 |
| | $AUC_{(0\text{-}24,\ day\ 1)}$ | (ng*h/mL) | 16 | 436 | 106 | 423 | 27.8 | 217 | 464 | 613 |
| **Day 5** | $C_{ss,max}$ | (ng/mL) | 16 | 181 | 72.5 | 165 | 50.1 | 48.3 | 165 | 300 |
| | $t_{ss,max}$ | (h) | 16 | – | – | – | – | 0.500 | 0.500 | 1.50 |
| | $C_{ss,min}$ | (ng/mL) | 16 | 4.40 | 1.57 | 4.16 | 35.1 | 2.38 | 4.37 | 8.51 |
| | $C_{ss,av}$ | (ng/mL) | 16 | 20.3 | 5.08 | 19.6 | 28.5 | 9.62 | 21.1 | 29.8 |
| | **DF** | (%) | 16 | 859 | 266 | 818 | 34.2 | 474 | 895 | 1237 |
| | $R_{ac(Cmax)}$ | | 16 | 0.956 | 0.273 | 0.921 | 28.9 | 0.559 | 0.857 | 1.52 |
| | $R_{ac(AUC)}$ | | 16 | 1.12 | 0.0813 | 1.11 | 7.18 | 1.02 | 1.1 | 1.26 |
| | $AUC_{ss,(0\text{-}24)}$ | (ng*h/mL) | 16 | 486 | 122 | 470 | 28.5 | 231 | 508 | 716 |

Treatment A - 5 mg dapagliflozin administered every 12 hours for 5 days; Treatment B - 10 mg dapagliflozin administered once a day for 5 days.
Treatment A, Day 5: the concentrations after the second dosing were used for PK parameter calculation if not otherwise specified.
AUC= Area under plasma concentration-time curve from zero to infinity; $AUC_{(0\text{-}12,\ day\ 1)}$ = Area under plasma concentration-time curve after first single dose administration on Day 1, ie. from time zero to 12 hours (Treatment A); $AUC_{(0\text{-}24,\ day\ 1)}$ = Area under plasma concentration-time curve after first single dose administration on Day 1, ie. from time zero to 24 hours (Treatment B); $AUC_{ss,(0\text{-}12)}$ = Area under plasma concentration-time curve at steady-state from time point zero until 12 hours post-dose (derived from data after first dosing on Day 5) (Treatment A); $AUC_{ss,(12\text{-}24)}$ = Area under plasma concentration-time curve at steady-state from time point 12 until 24 hours post-dose (derived from data after second dosing on Day 5) (Treatment A); $AUC_{ss,(0\text{-}24)}$ = Area

under plasma concentration-time curve at steady-state from time point zero until 24 hours post-dose (for Treatment A: the sum of $AUC_{ss,(0-12)}$ + $AUC_{ss,12-24)}$); $C_{max}$= maximum plasma (peak) drug concentration; $C_{ss,max}$ = Maximum plasma (peak) drug concentration at steady-state; $C_{ss,min}$ = Minimum (trough) steady-state drug concentration in plasma during dosing interval; $C_{ss,av}$ = The average plasma concentration at steady-state; DF = degree of fluctuation at steady-state; Rac = accumulation ratio; $R_{ac(Cmax)}$ = $C_{ss,max}$ on Day 5 / $C_{max}$ on Day 1; $R_{ac(AUC)}$ = $AUC_{ss,(12-24)}$ on Day 5 / $AUC_{(0-12, day\ 1)}$ (Treatment A) and $R_{ac(AUC)}$ = $AUC_{ss,(0-24)}$ on Day 5 / $AUC_{(0-24, day\ 1)}$ (Treatment B); $t_{ss,max}$= time of the maximum plasma concentration at steady-state.

Systemic exposure to dapagliflozin following dapagliflozin 5 mg every 12 hours and 10 mg once a day at steady-state was compared based on $AUC_{ss,(0-24)}$, $C_{ss,max}$ $C_{ss,min}$ and $C_{ss,av}$ applying a mixed model ANOVA and the results are shown in Table S3.

**Table S3 Statistical analysis of the exposure to dapagliflozin at steady-state following dapagliflozin 5 mg every 12 hours and dapagliflozin 10 mg once a day – PK analysis set**

| PK Parameter | | Dapagliflozin 5 mg every 12 hours | | Dapagliflozin 10 mg once a day | | Dapagliflozin 5 mg every 12 hours vs. 10 mg once a day | |
|---|---|---|---|---|---|---|---|
| | Unit | LSmean | 95% CI | LSmean | 95% CI | Ratio | 90% CI |
| **$AUC_{ss,(0-24)}$** | (ng*h/mL) | 458 | 397; 529 | 470 | 407; 543 | 0.975 | 0.949; 1.00 |
| **$C_{ss,max}$** | (ng/mL) | 79.6 | 64.0; 99.0 | 165 | 133; 205 | 0.483 | 0.425; 0.548 |
| **$C_{ss,min}$** | (ng/mL) | 6.76 | 5.77; 7.93 | 4.16 | 3.55; 4.88 | 1.62 | 1.47; 1.79 |
| **$C_{ss,av}$** | (ng/mL) | 18.9 | 16.3; 21.7 | 19.6 | 17.0; 22.6 | 0.962 | 0.931; 0.994 |

Treatment A - 5 mg dapagliflozin administered every 12 hours for 5;
Treatment B - 10 mg dapagliflozin administered once daily for 5 days.
$AUC_{ss,(0-24)}$ = Area under plasma concentration-time curve at steady-state from time point zero until 24 hours post-dose; CI= confidence interval; $C_{ss,av}$ = The average plasma concentration at steady-state; $C_{ss,max}$ = Maximum plasma (peak) drug concentration at steady-state; $C_{ss,min}$ = Minimum (trough) steady-state drug concentration in plasma during dosing interval; LSmean= least square mean.

The ANOVA of the derived PK variables characterising plasma exposure to dapagliflozin demonstrated no significant difference in $AUC_{ss,(0-24)}$ between the treatments. The geometric mean ratio for $AUC_{ss,(0-24)}$ was very close to unity, which was included in the corresponding 90% CI. The CI boundaries were within the limits of bioequivalence [0.8:1.25]. $C_{ss,max}$ was significantly lower and $C_{ss,min}$ was significantly higher following dapagliflozin 5 mg every 12 hours compared with dapagliflozin 10 mg once a day. The geometric mean ratio for $C_{ss,av}$ was close to unity, but the corresponding 90% CI was slightly below 1.

**Summary of pharmacodynamic results**

The IRGRA(%) over 24 hours following dapagliflozin 5 mg every 12 hours versus 10 mg once a day at steady-state (Day 5) was compared applying a mixed ANOVA model and the result is shown in Table S4.

**Table S4** **Statistical analysis (ANOVA) of the inhibition of renal glucose re-absorption over 24 hours following dapagliflozin 5 mg every 12 hours and dapagliflozin 10 mg once a day at steady-state (Day 5) – PD analysis set**

| Parameter | Dapagliflozin 5 mg every 12 hours | | Dapagliflozin 10 mg once a day | | Dapagliflozin 5 mg every 12 hours vs. 10 mg once a day | |
|---|---|---|---|---|---|---|
| | LSmean | 95% CI | LSmean | 95% CI | Ratio | 90% CI |
| IRGRA (%) | 34.4 | 29.1; 40.7 | 32.2 | 27.2; 38.0 | 1.07 | 0.947; 1.21 |

IRGRA(%) = Percent inhibition of renal glucose re-absorption over 24 hours. IRGRA(%) unit is [%*1.73$m^2$].

The ANOVA of IRGRA(%) demonstrated no significant difference between the treatments, ie following the same daily dose of dapagliflozin either given as 5 mg every 12 hours or as 10 mg once a day at steady-state, the ratio of the geometric means was very close to unity which was enclosed in the 90% CI. There was also no significant difference determined by non-parametric analysis providing the Hodges-Lehmann estimator of the difference between the medians of IRGRA(%).

The total urinary glucose excretion over 24 hours following dapagliflozin 5 mg every 12 hours versus 10 mg once a day at steady-state was compared applying a mixed ANOVA model and the result is shown in Table S5.

**Table S5** **Statistical analysis (ANOVA) of the total urinary glucose excretion over 24 hours following dapagliflozin 5 mg every 12 hours and dapagliflozin 10 mg once a day at steady-state (Day 5) – PD analysis set**

| Parameter | Dapagliflozin 5 mg every 12 hours | | Dapagliflozin 10 mg once a day | | Dapagliflozin 5 mg every 12 hours vs. 10 mg once a day | |
|---|---|---|---|---|---|---|
| | LSmean | 95% CI | LSmean | 95% CI | Ratio | 90% CI |
| $UGluc_{24h}$ (mmol) | 69.0 | 40.3; 118 | 58.4 | 34.1; 100.0 | 1.18 | 0.626; 2.23 |

$UGluc_{24h}$ = Amount of glucose excreted over 24 hours.

The ANOVA of $UGluc_{24}$ demonstrated no significant difference between the treatments, ie following the same daily dose of dapagliflozin either given as 5 mg every 12 hours or as 10 mg once a day at steady-state, the ratio of the geometric means was close to unity which was enclosed in the 90% CI.

The results of the ANCOVAs of $AUE_{0-180}$ of glucose and insulin after each meal with baseline as covariate are shown in Table S6 for glucose and in Table S7 for insulin.

**Table S6** **Statistical analysis (ANCOVA) of the $AUE_{(0-180)}$ of glucose following dapagliflozin 5 mg every 12 hours and dapagliflozin 10 mg once a day at steady-state (Day 5) – PD analysis set**

| Parameter | Dapagliflozin 5 mg every 12 hours | | Dapagliflozin 10 mg once a day | | Dapagliflozin 5 mg every 12 hours vs. 10 mg once a day | |
|---|---|---|---|---|---|---|
| | LSmean | 95% CI | LSmean | 95% CI | Ratio | 90% CI |
| **Glucose $AUE_{(0-180)}$** (mmol·h/L) | | | | | | |
| Breakfast | 17.3 | 16.1; 18.5 | 17.4 | 16.2; 18.6 | 0.994 | 0.949; 1.04 |
| Lunch | 18.5 | 16.8; 20.3 | 18.4 | 16.7; 20.2 | 1.00 | 0.902; 1.12 |
| Dinner | 19.9 | 18.9; 21.0 | 19.8 | 18.8; 20.9 | 1.01 | 0.980; 1.03 |

AUE = Area under the effect time curve form time point zero until 180 minutes post meal.
Source: Table 11.2.9.1

**Table S7** **Statistical analysis (ANCOVA) of the $AUE_{0-180}$ of insulin following dapagliflozin 5 mg every 12 hours and dapagliflozin 10 mg once a day at steady-state (Day 5) – PD analysis set**

| Parameter | Dapagliflozin 5 mg every 12 hours | | Dapagliflozin 10 mg once a day | | Dapagliflozin 5 mg every 12 hours vs. 10 mg once a day | |
|---|---|---|---|---|---|---|
| | LSmean | 95% CI | LSmean | 95% CI | Ratio | 90% CI |
| **Insulin $AUE_{0-180}$** (mmol·h/L) | | | | | | |
| Breakfast | 133 | 113; 157 | 142 | 120; 167 | 0.939 | 0.829; 1.06 |
| Lunch | 52.0 | 44.5; 60.7 | 61.8 | 52.9; 72.2 | 0.841 | 0.761; 0.929 |
| Dinner | 82.5 | 68.0; 100 | 79.3 | 65.3; 96.2 | 1.04 | 0.906; 1.20 |

AUE = Area under the effect time curve form time point zero until 180 minutes post meal.
Source: Table 11.2.9.1

The ANCOVAs of $AUE_{0-180}$ of glucose and insulin after breakfast, lunch and dinner demonstrated no significant differences between the treatments, except for $AUE_{0-180}$ of insulin after lunch, ie following the same daily dose of dapagliflozin either given as 5 mg every 12 hours or as 10 mg once a day at steady-state.

The results of the ANOVA comparing the change in GIP plasma concentrations (post-meal – pre-meal) is shown in Table S8.

**Table S8** **Statistical analysis (ANOVA) of change in GIP plasma concentrations (post-meal – pre-meal) following dapagliflozin 5 mg every 12 hours and dapagliflozin 10 mg once a day at steady-state (Day 5) – PD analysis set**

| Parameter | Dapagliflozin 5 mg every 12 hours | | Dapagliflozin 10 mg once a day | | Dapagliflozin 5 mg every 12 hours vs. 10 mg once a day | |
|---|---|---|---|---|---|---|
| | LSmean | 95% CI | LSmean | 95% CI | Ratio | 90% CI |
| **GIP** (pg/mL) | | | | | | |
| Dinner | 106 | 74.4; 150 | 133 | 94.0: 189 | 0.791 | 0.587; 1.07 |

GIP = Glucose-dependent insulinotropic polypeptide

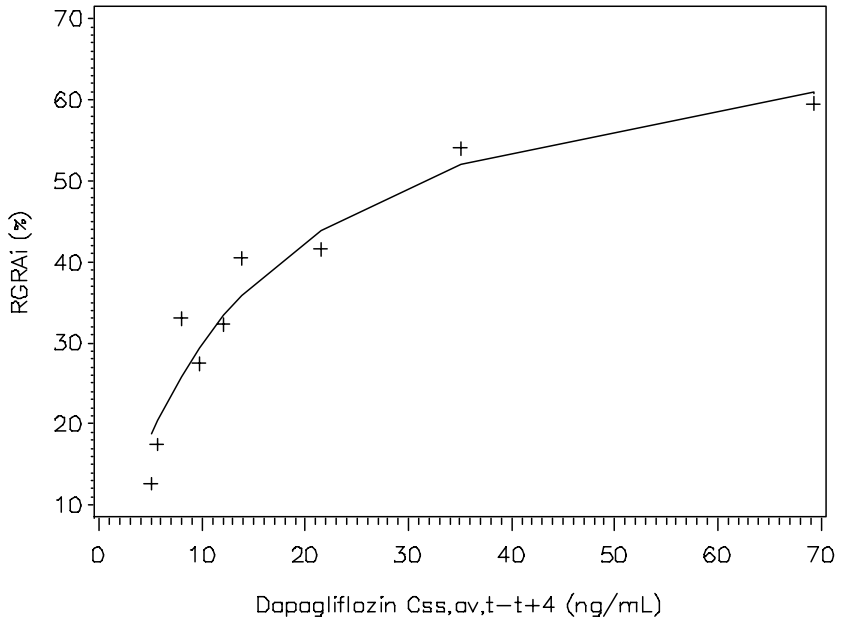
The ANOVA of the change in GIP plasma concentrations (post-meal – pre-meal) for dinner provided a value of 0.791 for the point estimate of the ratio dapagliflozin 5 mg every 12 hours vs. dapagliflozin 10 mg once a day. This may indicate a tendency to a lower GIP plasma concentration following the 5 mg dose administered every 12 hours relative to the 10 mg dose administered once a day at steady state. However, unity was enclosed in the 90% CI of the ANOVA and similar results were obtained applying a t-test ($p = 0.3005$) and a non-parametric analysis using a Wilcoxon-test ($p = 0.5633$). However, the study was not planned to show a statistically significant difference in GIP plasma concentrations between the treatments.

Overall, and with emphasis on dinner, no consistent evidence for an inhibition of the rate of gut glucose absorption was obtained.

**Summary of pharmacokinetic/pharmacodynamic relationships**

A non-linear regression model was used to delineate the relationship between the mean dapagliflozin plasma concentrations and % inhibition of renal glucose re-absorption over the 4-hours intervals. The scatter plot and the fit to the model between mean dapagliflozin plasma concentrations and RGRAi are shown in Figure S2.

**Figure S2 Scatter plot between mean dapagliflozin plasma concentration and $IRGRA_i$(%)– PD analysis set**




Treatment A - 5 mg dapagliflozin administered every 12 hours for 5 days;
Treatment B - 10 mg dapagliflozin administered once daily for 5 days.
$IRGRA_i$(%) = Percent inhibition of renal glucose re-absorption over an interval. The following non-linear regression model was used to fit the data: $IRGRA_i(\%) = E0 + (E_{max} * C_{ss,av})/ (EC_{50} + C_{ss,av})$

According to the fit of $IRGRA_i$(%) over an interval to the non-linear regression model an $EC_{50}$ for $IRGRA_i$(%) was achieved at average dapagliflozin plasma concentrations of 14.72 ng/mL with an $E_{max}$ of 73.95 %.

**Summary of safety results**

Administration of dapagliflozin 5 mg every 12 hours and 10 mg once a day over 5 days was safe and was well tolerated. Altogether, 5 of 16 subjects reported 10 AEs which were all of mild to moderate intensity. The most common treatment-emergent AE was back pain, reported each by 1 subject per treatment. All other AEs were reported not more frequently than by 1 subject. The majority of AEs was considered by the Investigator not to be related to the IPs. There were no relevant differences between the profiles and the incidences of AEs reported for each treatment.

Mean plasma urate concentrations decreased upon both treatments and all 16 subjects showed urate levels below normal upon 4 days under treatment with dapagliflozin 5 mg every 12 hours and 10 mg once a day.

Glucose signals in urinalysis above normal were observed in all subjects at the end of both treatment periods, consistent with the pharmacological action of dapagliflozin following multiple dosing.

There were no clinically relevant changes in clinical laboratory, vital sign and ECG parameters and upon physical examination.