Clinical Study Reports Summary	
Product	XIGDUO™ XR
Study Code	D1691C00016

Clinical Study Reports Summary

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1 SUMMARY

During the period of 16 January 2018 to 15 January 2019, 4 study reports for clinical pharmacology studies (all for Study D1691C00016) were signed off and released for XIGDUO™ XR[1] (dapagliflozin + metformin hydrochloride extended release [XR]).

This study was conducted to establish, according to Brazilian regulatory requirements, the bioequivalence of dapagliflozin/metformin XR 5/500 mg and 10/1000 mg tablets manufactured at a Humacao plant in Puerto Rico and dapagliflozin/metformin XR 5/500 mg and 10/1000 mg tablets manufactured at a Mount Vernon plant in United States. This study supports the transfer of manufacturing processes of Xigduo XR tablets to the Mount Vernon plant.

The current recommendation is to administer Xigduo XR with food; therefore, bioequivalence was evaluated under fasting and fed conditions. This study had 4 parts (Parts 1, 2, 3, and 4), and this NDA update provides results from all parts of the study.

Part 1 (PBIO014/16): Dapagliflozin/metformin XR 5/500 mg (manufactured at a Mount Vernon plant [test product]) and dapagliflozin/metformin XR 5/500 mg (manufactured at a Humacao plant [reference product]) under fed conditions.

Part 2 (PBIO034/17): Dapagliflozin/metformin XR 5/500 mg (manufactured at a Mount Vernon plant [test product]) and dapagliflozin/metformin XR 5/500 mg (manufactured at a Humacao plant [reference product]) under fasting conditions.

Part 3 (PBIO015/16): Dapagliflozin/metformin XR 10/1000 mg (manufactured at a Mount Vernon plant [test product]) and dapagliflozin/metformin XR 10/1000 mg (manufactured at a Humacao plant [reference product]) under fed conditions.

Part 4 (PBIO035/17): Dapagliflozin/metformin XR 10/1000 mg (manufactured at a Mount Vernon plant [test product]) and dapagliflozin/metformin XR 10/1000 mg (manufactured at a Humacao plant [reference product]) under fasting conditions.

[1] XIGDUO XR (dapagliflozin/metformin XR) is a trademark of the AstraZeneca group of companies.

1.1 A four-part bioequivalence study to compare two fixed-dose combination (FDC) tablets of dapagliflozin/metformin XR 5/500 mg (Part 1 and 2) and 10/1000 mg (Part 3 and 4) manufactured at two different plants (Humacao, Puerto Rico and Mount Vernon, US) in healthy subjects under fasting and fed conditions – Part 1

1.1.1 Objectives

Objectives and outcome measures associated with Study D1691C00016 – Part 1 are presented below.

Primary objectives for Part 1:

- To demonstrate the bioequivalence of dapagliflozin/metformin XR 5/500 mg tablets manufactured at the Mount Vernon plant in US and dapagliflozin/metformin XR 5/500 mg tablets manufactured at the Humacao plant in Puerto Rico under fed conditions.

Secondary objectives for Part 1:

- To characterize and compare pharmacokinetic (PK) profiles of dapagliflozin and metformin administered as a dapagliflozin and metformin 5/500 mg fixed-dose combination (FDC) formulation under fed conditions.
- To thoroughly evaluate the safety of single doses of dapagliflozin/metformin 5/500 mg in healthy subjects under fed conditions.

1.1.2 Study design

Study D1691C00016 was an open-label, randomized, 4-part, 2-treatments per part, crossover 2 × 2 study. Seventy-two subjects (males and females) ranging from 18 to 50 years old were randomized into each of the 4 parts for a total of 288 subjects. The study was conducted at a single study site, and each part was conducted independently. On each period, subjects received the test formulation or the reference formulation.

Part 1 of the study included a maximum screening period of 60 days followed by 2 treatment periods, a washout period between the administration of each dose, and an end-of-study (EOS) visit.

Subjects were admitted to the site and received an evening meal the night before administration of dapagliflozin/metformin XR (Day -1). On Day 1, subjects assigned to a fed treatment were fasted for at least 8 hours prior to a standard breakfast, given approximately 30 minutes before dosing. No fluids were allowed apart from water, which could be given up to 1 hour prior to dosing and 2 hours after dosing (excludes water given during investigational product [IP] administration). For Part 1, 72 subjects were randomized into the treatment sequences shown in Table 1:

Table 1 Treatment Sequence for Part 1 of Study D1691C00016

	Conditions in fed state	
Treatment period	1	2
Sequence 1 (n=36)	A	B
Sequence 2 (n=36)	B	A

Treatment A consists of administration of dapagliflozin/metformin XR 5/500 mg test tablets under a fed state
Treatment B consists of administration of dapagliflozin/metformin XR 5/500 mg reference tablets under fed state
n number of subjects

On each treatment period, subjects received an oral dose of the reference drug (dapagliflozin 5 mg/metformin 500 mg manufactured in Humacao, Puerto Rico) or the test drug (dapagliflozin 5 mg/metformin 500 mg manufactured in Mount Vernon, US) together with 200 mL of water.

Subjects remained at the site for at least 12 hours and were discharged on the night of Day 1. Subjects were expected to return for additional collections on Day 2 (morning and night), Day 3 (morning), and Day 4 (morning). Breakfast was offered to the subjects during extra collections.

There was a washout period of 7 days between administrations of each dose. Treatments A and B were orally given once on each treatment period.

The EOS visit occurred approximately 72 hours after the last administration of dapagliflozin/metformin XR.

Subjects enrolled in the study were male and female subjects aged 18 to 50 years old; body mass index (BMI) between 18.50 and 24.90 kg/m^2, inclusive, with a range of 15% on the upper limit being permitted (ie, up to 28.63 kg/m^2); and weigh between 50 and 100 kg, inclusive, at screening.

For Part 1 of the study, the participation of 72 subjects (36 male and 36 female subjects) aged 18 to 50 years old was anticipated. Due to dropouts and exclusions before IP administration for the first period, 76 subjects (39 male and 37 female subjects) had to be selected. Three subjects withdrew their participation in the study, and 1 subject was excluded. These subjects were replaced by subjects who followed the same randomization sequence.

In all, 72 healthy male and female subjects were randomized in Part 1. All 72 subjects received the assigned dose for period 1, and 21 subjects were withdrawn before administration of the assigned dose for period 2. As a result, 51 of the 72 subjects concluded both study periods. Two subjects were withdrawn from Part 1 due to AEs: 1 subject due to fever and myalgia and 1 subject due to symptoms of pain and use of a disallowed medication).

1.1.3 Statistical methods for bioequivalence evaluation

Pharmacokinetics (PK) parameters were obtained from the area under the plasma concentration-time curves (AUC) of the drugs and statistically analyzed for bioequivalence determination. The following PK parameters were determined: AUC from time zero to last quantifiable concentration "t" (AUC_{0-t}), AUC from time zero to infinity (AUC_{0-inf}), maximum (peak) concentration (C_{max}) of the drug and/or metabolite, and time to reach such peak (t_{max}).

For bioequivalence evaluation, an analysis of variance (ANOVA) using generalized linear models was used for PK analysis of AUC and C_{max}. The ANOVA model included the following fixed factors: sequence (or group), subjects within the sequence (intersubject trace), period, treatment or drug, and error (intrasubject trace). Two drugs are considered bioequivalent if the 90% confidence interval (90% CI) for the geometric mean ratio of parameters C_{max} and AUC_{0-t} (test/reference) each fall entirely within an 80% to 125% interval (data converted into natural logarithm [Ln]).

1.1.4 Results

1.1.4.1 Pharmacokinetics

Analysis by ANOVA indicated that bioavailability equivalence was attained between the treatments (Table 2). The bioavailability rule was attained for both dapagliflozin and metformin. The results also show that the geometric mean ratios determined for the treatments (test/reference) are well centered for all PK parameters evaluated (C_{max}, AUC_{0-t}, and AUC_{0-inf}). In addition, the estimated values for intrasubject coefficient of variation (CV_{intra}) were all lower than 20%. Consequently, the power of the test obtained via the two one-sided test (TOST) method achieved values close to 100% for the 3 parameters evaluated for dapagliflozin and metformin.

Table 2 Geometric means, confidence intervals, and p values obtained in the analysis of variance for dapagliflozin and metformin – Part 1

	Statistical Results by Pharmacokinetic Parameter		
Dapagliflozin	**C_{max}**	**AUC_{0-t}**	**AUC_{0-inf}**
Geometric means obtained by the least squares' method			
Comparator (B)	35.9706	228.9550	236.2907
Test (A)	37.5582	233.2389	241.4515
CIs (Shortest) obtained for ratio between the treatments (transformed data)			
Contrast	90% CI	90% CI	90% CI
A versus B (%)	98.39-110.81	99.86-103.92	100.06-104.36
Point estimates obtained for ratio between the treatments (%)			
A/B	104.41	101.87	102.18
Metformin	**C_{max}**	**AUC_{0-t}**	**AUC_{0-inf}**

Table 2 Geometric means, confidence intervals, and p values obtained in the analysis of variance for dapagliflozin and metformin – Part 1

	Statistical Results by Pharmacokinetic Parameter		
Geometric means obtained by the least squares' method			
Comparator (B)	580.9339	6105.2932	6289.5757
Test (A)	596.1621	6407.4084	6535.7751
CIs (Shortest) obtained for ratio between the treatments (transformed data)			
Contrast	90% CI	90% CI	90% CI
A versus B (%)	99.40-105.95	99.43-110.78	97.86-110.35
Point estimates obtained for ratio between the treatments (%)			
A/B	102.62	104.95	103.91

All 51 subjects who completed Part 1 of the study were included in the PK evaluation.

AUC_{0-t} area under the plasma concentration-time curve from zero to time of last quantifiable concentration; AUC_{0-inf} area under the plasma concentration-time curve from zero to infinity; CI confidence interval; C_{max} maximum (peak) plasma concentration of drug

Nonparametric analyses of t_{max} indicate that there is no significant difference at the 90% confidence level on the average time to reach maximum concentrations of both treatments evaluated, ie, dapagliflozin and metformin (test vs reference).

1.1.4.2 Safety

During the study, some subjects experienced adverse events (AEs); all AEs were mild and nonserious. The most frequent AE was leukocyturia. No serious adverse reactions occurred during this period. The adverse reactions that occurred had no consequence for the study.

Some prestudy clinical tests had results outside the reference range; however, these results were analyzed by the medical team in charge and were considered not clinically relevant.

1.2 A four-part bioequivalence study to compare two fixed dose combination (FDC) tablets of dapagliflozin/metformin XR 5/500 mg (Part 1 and 2) and 10/1000 mg (Part 3 and 4) manufactured at two different plants (Humacao, Puerto Rico and Mount Vernon, US) in healthy subjects under fasting and fed conditions – Part 2

1.2.1 Objectives

Objectives and outcome measures associated with Study D1691C00016 – Part 2 are presented below.

Primary objective for Part 2:

- To demonstrate the bioequivalence of dapagliflozin/metformin XR 5/500 mg tablets manufactured at the Mount Vernon plant and dapagliflozin/metformin XR 5/500 mg tablets manufactured at the Humacao plant, under fasting conditions.

Secondary objectives for Part 2:

- To characterize and compare PK profiles of dapagliflozin and metformin administered as a dapagliflozin and metformin 5/500 mg FDC formulation under fasting conditions.
- To thoroughly evaluate the safety of single doses of dapagliflozin/metformin 5/500 mg in healthy subjects under fasting conditions.

1.2.2 Study design

Study D1691C00016 was an open-label, randomized, 4-part, 2-treatments per part, crossover 2 × 2 study. Seventy-two subjects (males and females) ranging from 18 to 50 years old were randomized into each of the 4 parts for a total of 288 subjects. The study was conducted at a single study site, and each part was conducted independently. On each period, subjects received the test formulation or the reference formulation.

Part 2 of the study included a maximum screening period of 60 days followed by 2 treatment periods, a washout period between administration of each dose, and an EOS visit.

Subjects were admitted to the site and received an evening meal the night before administration of dapagliflozin/metformin XR (Day -1). On Day 1, subjects assigned to a fasting state were fasted for at least 8 hours prior to dosing and until 4 hours after dosing. No fluids were allowed apart from water, which could be given up to 1 hour prior to dosing and 2 hours after dosing (excluding water given during IP administration). For Part 2, 72 subjects were randomized into the treatment sequences shown in Table 3:

Table 3 Treatment Sequence for Part 2 of Study D1691C00016

	Conditions in fasted state	
Treatment period	1	2
Sequence 1 (n=36)	A	B
Sequence 2 (n=36)	B	A

Treatment A consists of administration of dapagliflozin/metformin XR 5/500 mg test tablets under a fasted state.

Treatment B consists of administration of dapagliflozin/metformin XR 5/500 mg reference tablets under a fasted state.

n number of subjects

On each treatment period, subjects received an oral dose of the reference drug (dapagliflozin 5 mg/metformin 500 mg manufactured in Humacao, Puerto Rico) or the test drug (dapagliflozin 5 mg/metformin 500 mg manufactured in Mount Vernon, US) together with 200 mL of water.

Subjects remained at the site for at least 12 hours and were discharged on the night of Day 1. Subjects were expected to return for additional collections on Day 2 (morning and night), Day 3 (morning), and Day 4 (morning). Breakfast was offered to the subjects during extra collections.

There was a washout period of 7 days between administrations of each dose. Treatments A and B were given once on each treatment period.

The EOS visit occurred approximately 72 hours after the last administration of dapagliflozin/metformin XR.

Subjects enrolled in the study were male and female subjects aged 18 to 50 years old; BMI between 18.50 and 24.90 kg/m^2, inclusive, with a range of 15% on the upper limit being permitted (ie, up to 28.63 kg/m^2)]; and weigh between 50 and 100 kg, inclusive, at screening.

For Part 2 of the study, the participation of 72 subjects (36 male and 36 female subjects) aged 18 to 50 years old was anticipated. Due to dropouts and exclusions before IP administration for the first period, 77 subjects (39 male and 38 female subjects) had to be selected. One subject withdrew his participation in the study, and 4 subjects were excluded. These subjects were replaced by subjects who followed the same randomization sequence.

In all, 72 healthy male and female subjects were randomized in Part 2. Of these, 71 subjects received the assigned dose for period 1, and 1 subject did not receive any treatment (subject freely withdrew for personal reasons). Twenty of the 71 subjects who were dosed in period 1 were withdrawn before receiving the assigned treatment for period 2. As a result, only 51 of the 72 subjects concluded both study periods. Two subjects were withdrawn from Part 1 due to AEs: 1 subject due to a motorcycle accident and 1 subject due to watery feces.

1.2.3 Statistical methods for bioequivalence evaluation

A brief summary of statistical methods is provided in Section 1.1.3.

1.2.4 Results

1.2.4.1 Pharmacokinetics

Analysis by ANOVA indicated that bioavailability equivalence was attained between the treatments (Table 4). The bioavailability rule was attained for both dapagliflozin and metformin. The results also show that the geometric mean ratios of the treatments (test/reference) are well centered for all PK parameters evaluated (C_{max}, AUC_{0-t}, and AUC_{0-inf}). In addition, the estimated values for intrasubject coefficient of variation (CV_{intra}) were all lower than 21%. Consequently, the power of the test obtained via the TOST method achieved values close to 100% for the 3 parameters evaluated for dapagliflozin and metformin.

Table 4 Geometric means, confidence intervals, and p values obtained in the analysis of variance for dapagliflozin and metformin – Part 2

	Statistical Results by Pharmacokinetic Parameter		
Dapagliflozin	**C_{max}**	**AUC_{0-t}**	**AUC_{0-inf}**
Geometric Means obtained by the least squares' method			
Comparator (B)	57.5871	217.6314	225.4169
Test (A)	57.5177	228.3929	236.8268
CIs (Shortest) obtained for ratio between the treatments (transformed data)			
Contrast	90% CI	90% CI	90% CI
A versus B (%)	93.30-106.93	102.87-107.06	102.95-107.21
Point estimates obtained for ratio between the treatments (%)			
A/B	99.88	104.94	105.06
Metformin	**C_{max}**	**AUC_{0-t}**	**AUC_{0-inf}**
Geometric Means obtained by the least squares' method			
Comparator (B)	557.1759	4315.6188	4466.6382
Test (A)	560.0266	4379.0728	4541.0678
CIs (Shortest) obtained for ratio between the treatments (transformed data)			
Contrast	90% CI	90% CI	90% CI
A versus B (%)	93.92-107.57	95.41-107.91	95.57-108.15
Point estimates obtained for ratio between the treatments (%)			
A/B	100.51	101.47	101.67

All 51 subjects who completed Part 2 of the study were included in the PK evaluation.

AUC_{0-t} area under the plasma concentration-time curve from zero to time of last quantifiable concentration; AUC_{0-inf} area under the plasma concentration-time curve from zero to infinity; CI confidence interval; C_{max} maximum (peak) plasma concentration of drug

Nonparametric analyses of t_{max} indicate that there is no significant difference at the 90% confidence level on the average time to reach maximum concentrations of both treatments evaluated, ie, dapagliflozin and metformin (test vs reference).

1.2.4.2 Safety

During the study, some subjects experienced AEs. Most AEs were mild, and all were nonserious. Two subjects had AEs of moderate severity; both subjects had an AE of headache suspected as being related to IP by the investigator. The most frequent AE was leukocyturia. No serious adverse reactions occurred during this period. The adverse reactions that occurred had no consequence for the study.

Some prestudy clinical tests had results outside the reference range; however, these results were analyzed by the medical team in charge and were considered not clinically relevant.

1.3 A four-part bioequivalence study to compare two fixed dose combination (FDC) tablets of dapagliflozin/metformin XR 5/500 mg (Part 1 and 2) and 10/1000 mg (Part 3 and 4) manufactured at two different plants (Humacao, Puerto Rico and Mount Vernon, US) in healthy subjects under fasting and fed conditions – Part 3

1.3.1 Objectives

Objectives and outcome measures associated with Study D1691C00016 – Part 3 are presented below.

Primary objective for Part 3:

- To demonstrate the bioequivalence of dapagliflozin/metformin XR 10/1000 mg tablets manufactured at the Mount Vernon plant and dapagliflozin/metformin XR 10/1000 mg tablets manufactured at the Humacao plant under fed conditions.

Secondary objectives for Part 3:

- To characterize and compare PK profiles of dapagliflozin and metformin administered as a dapagliflozin/metformin XR 10/1000 mg FDC formulation under fed conditions.
- To thoroughly evaluate the safety of single doses of dapagliflozin/metformin 10/1000 mg in healthy subjects under fed conditions.

1.3.2 Study design

The study design of Part 3 was similar to the design of Part 1 (Section 1.1.2), but the 72 subjects were randomized into the treatment sequences shown in Table 5:

Table 5 Treatment Sequence for Part 3 of Study D1691C00016

	Conditions in fed state	
Treatment period	1	2
Sequence 1 (n=36)	C	D
Sequence 2 (n=36)	D	C

Treatment C consists of administration of dapagliflozin/metformin XR 10/1000 mg test tablets under a fed state.

Treatment D consists of administration of dapagliflozin/metformin XR 10/1000 mg reference tablets under fed state.

n number of subjects

For Part 3 of the study, the participation of 72 subjects (36 male and 36 female subjects) aged 18 to 50 years old was anticipated. Due to dropouts and exclusions before drug administration for the first period, 75 subjects (36 male and 39 female subjects) had to be selected. Three subjects were excluded. These subjects were replaced by subjects who followed the same randomization sequence.

In all, 72 healthy male and female subjects were randomized in Part 3. All 72 subjects received the assigned dose for period 1; 23 subjects were withdrawn before administration of the assigned dose for period 2. As a result, only 49 of the 72 subjects concluded both study periods. Four subjects were withdrawn from Part 1 due to AEs: 2 subjects due to diarrhea and 2 subjects due to vomiting.

1.3.3 Statistical methods for bioequivalence evaluation

A brief summary of statistical methods is provided in Section 1.1.3.

1.3.4 Results

1.3.4.1 Pharmacokinetics

Analysis by ANOVA indicated that bioavailability equivalence was attained between treatments (Table 6). The bioavailability rule was attained for both dapagliflozin and metformin.

Dapagliflozin data show that AUC_{0-t} and AUC_{0-inf} (test/reference) exhibited well-centered estimates for mean ratios, low CV_{intra} (lower than 8%), and high test power (100%). However, the ratio for C_{max} was slightly shifted up (above 111%), indicating higher values for test product than for reference product. Estimated CV_{intra} was above 23% and, although not considered high, the test power achieved by the TOST method, which is mainly influenced by ratio shift, did not achieve the minimum value of 80% required by the Brazilian Health Surveillance Agency (ie, Agencia Nacional de Vigilancia Sanitaria [ANVISA]). Based on this result (~78% test power for C_{max}), an intrasubject variance equality test was performed. In addition, because the equality hypothesis was rejected at a significance level of 5%, variance

equivalence was chosen to be demonstrated. Both tests have been proposed by Chow and Liu[2]. The variance equality test at a significance level of 5% supports equivalence of both treatments (test/reference) with respect to intrasubject variability. Therefore, treatments are bioequivalent for mean values and variance.

With respect to metformin results, PK data show that the geometric mean ratios for C_{max}, AUC_{0-t}, and AUC_{0-inf} are well centered for both treatments (test/reference). In addition, estimated values for CV_{intra} were all lower than 18%. Consequently, the power of the test obtained via the TOST method was 100% for all 3 PK parameters measured.

Table 6 Geometric means, confidence intervals, and p values obtained in the analysis of variance for dapagliflozin and metformin – Part 3

	Statistical Results by Pharmacokinetic Parameter		
Dapagliflozin	**C_{max}**	**AUC_{0-t}**	**AUC_{0-inf}**
Geometric Means obtained by the least squares' method			
Comparator (D)	67.8323	460.6121	475.6780
Test (C)	75.6857	463.1423	475.3730
CIs (Shortest) obtained for ratio between the treatments (transformed data)			
Contrast	90% CI	90% CI	90% CI
C versus D (%)	103.20-120.64	98.36-102.79	97.35-102.59
Point estimates obtained for ratio between the treatments (%)			
C/D	111.58	100.55	99.94
Metformin	**C_{max}**	**AUC_{0-t}**	**AUC_{0-inf}**
Geometric Means obtained by the least squares' method			
Comparator (D)	972.3598	10407.9683	10731.9481
Test (C)	973.3140	10111.4263	10405.2680
CIs (Shortest) obtained for ratio between the treatments (transformed data)			
Contrast	90% CI	90% CI	90% CI
C versus D (%)	95.01-105.46	91.73-102.89	91.84-102.36
Point estimates obtained for ratio between the treatments (%)			
C/D	100.10	97.15	96.96

All 49 subjects who completed Part 3 of the study were included in the PK evaluation.

AUC_{0-t} area under the plasma concentration-time curve from zero to time of last quantifiable concentration; AUC_{0-inf} area under the plasma concentration-time curve from zero to infinity; CI confidence interval; C_{max} maximum (peak) plasma concentration of drug

[2] Chow SC, Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. 2nd ed. NewYork: Marcel Dekker; 2000. p. 584

Nonparametric analysis of t_{max} showed significant differences at the 90% confidence level for dapagliflozin but not for metformin (test vs reference).

1.3.4.2 Safety

During the study, some subjects experienced AEs; all AEs were mild and nonserious. The most common AE was leukocyturia. No serious adverse reactions occurred during this period. The adverse reactions that occurred had no consequence for the study.

Some prestudy clinical tests had results outside the reference range; however, these results were analyzed by the medical team in charge and were considered not clinically relevant.

1.4 A four-part bioequivalence study to compare two fixed dose combination (FDC) tablets of dapagliflozin/metformin XR 5/500 mg (Part 1 and 2) and 10/1000 mg (Part 3 and 4) manufactured at two different plants (Humacao, Puerto Rico and Mount Vernon, US) in healthy subjects under fasting and fed conditions – Part 4

1.4.1 Objectives

Objectives and outcome measures associated with Study D1691C00016 – Part 4 are presented below.

Primary objective for Part 4:

- To demonstrate the bioequivalence of dapagliflozin/metformin XR 10/1000 mg tablets manufactured at the Mount Vernon plant and dapagliflozin/metformin XR 10/1000 mg tablets manufactured at the Humacao plant, under fasting conditions.

Secondary objectives for Part 4:

- To characterize and compare PK profiles of dapagliflozin and metformin administered as a dapagliflozin/metformin 10/1000 mg FDC formulation under fasting conditions.
- To thoroughly evaluate the safety of single doses of dapagliflozin/metformin 10/1000 mg in healthy subjects under fasting conditions.

1.4.2 Study design

The study design of Part 4 was similar to the design of Part 2 (Section 1.2.2) but the 72 subjects were randomized into the treatment sequences shown in Table 7:

Table 7 Treatment Sequence for Part 4 of Study D1691C00016

	Conditions in fasted state	
Treatment period	1	2
Sequence 1 (n=36)	C	D

Table 7 Treatment Sequence for Part 4 of Study D1691C00016

	Conditions in fasted state	
Sequence 2 (n=36)	D	C

Treatment C consists of administration of dapagliflozin/metformin XR 10/1000 mg test tablets under a fasted state.

Treatment D consists of administration of dapagliflozin/metformin XR 10/1000 mg reference tablets under fasted state.

n number of subjects

For Part 4 of the study, the participation of 72 subjects (36 male and 36 female subjects) aged 18 to 50 years old was anticipated. Due to dropouts and exclusions before drug administration for the first period, 79 subjects (39 male and 40 female subjects) had to be selected. Five subjects withdrew their participation in the study, and 2 subjects were excluded. These subjects were replaced by subjects who followed the same randomization sequence.

In all, 72 healthy male and female subjects were randomized in Part 4. Of these, 69 subjects received the assigned dose for period 1. Three subjects were excluded during the preadmission visit (Period 1) and did not receive any treatment. These subjects could not be replaced due to reservation unavailability. Twenty-eight of the 69 subjects who were dosed in period 1 were withdrawn before receiving the assigned treatment for period 2. As a result, only 41 of the 72 subjects concluded both study periods. Six subjects were withdrawn from Part 1 due to AEs: 2 subjects due to diarrhea, 1 subject due to rhinorrhea, epigastric pain, and asthenia; 1 subject due to an allergic reaction; 1 subject due to vomiting; and 1 subject due odynophagia, retro-ocular pain, and fever.

1.4.3 Statistical methods for bioequivalence evaluation

A brief summary of statistical methods is provided in Section 1.1.3.

1.4.4 Results

1.4.4.1 Pharmacokinetics

Analysis by ANOVA indicated that bioavailability equivalence was attained between the treatments (Table 8). The bioavailability rule was attained for both dapagliflozin and metformin. The results also show that the geometric mean ratios of the treatments (test/reference) are well centered for all PK parameters evaluated (C_{max}, AUC_{0-t}, and AUC_{0-inf}) and estimated values of CV_{intra} were all lower than 24%. Consequently, the power of the test obtained via the TOST method achieved values close to 100% for the 3 parameters evaluated for dapagliflozin and metformin.

Table 8 Geometric means, confidence intervals, and p values obtained in the analysis of variance for dapagliflozin and metformin – Part 4

	Statistical Results by Pharmacokinetic Parameter		
Dapagliflozin	**C_{max}**	**AUC_{0-t}**	**AUC_{0-inf}**
Geometric means obtained by the least squares' method			
Comparator (D)	119.2934	461.5072	473.1552
Test (C)	117.3056	458.0950	472.0699
CIs (Shortest) obtained for ratio between the treatments (transformed data)			
Contrast	90% CI	90% CI	90% CI
C versus D (%)	91.79-105.34	97.06-101.51	97.43-102.17
Point estimates obtained for ratio between the treatments (%)			
C/D	98.33	99.26	99.77
Metformin	**C_{max}**	**AUC_{0-t}**	**AUC_{0-inf}**
Geometric means obtained by the least squares' method			
Comparator (D)	930.0847	7402.2830	7738.2003
Test (C)	948.0217	7535.9224	7825.4384
CIs (Shortest) obtained for ratio between the treatments (transformed data)			
Contrast	90% CI	90% CI	90% CI
C versus D (%)	93.61-110.99	94.43-109.76	94.16-108.61
Point estimates obtained for ratio between the treatments (%)			
C/D	101.93	101.81	101.13

All 41 subjects who completed Part 4 of the study were included in the PK evaluation.

AUC_{0-t} area under the plasma concentration-time curve from zero to time of last quantifiable concentration; AUC_{0-inf} area under the plasma concentration-time curve from zero to infinity; CI confidence interval; C_{max} maximum (peak) plasma concentration of drug

Nonparametric analyses of t_{max} indicate that there is no significant difference at the 90% confidence level on the average time to reach maximum concentrations of both treatments evaluated, ie, dapagliflozin and metformin (test vs reference).

1.4.4.2 Safety

During the study, some subjects experienced AEs. Most AEs were mild, and all were nonserious. Three subjects had AEs of moderate severity: 2 subjects had an AE of headache, and 1 subject had AEs of pruritus and hyperemia. All events were suspected as being related to IP by the investigator. The most common AE was leukocyturia. No serious adverse reactions occurred during this period. The adverse reactions that occurred had no consequence for the study.

Some prestudy clinical tests had results outside the reference range; however, these results were analyzed by the medical team in charge and were considered not clinically relevant.