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Name of Active Ingredient: Ipragliflozin		

SYNOPSIS

Title of Study: An Exploratory Study to Investigate the Effects of Ipragliflozin (ASP1941) on Glucose Homeostasis and Urinary Glucose Excretion in Healthy Subjects and Subjects with Type 2 Diabetes Mellitus (T2DM)

Investigators/Coordinating Investigator: Principal Investigator of this study was PD Dr. med. [redacted], Germany.

Study Center(s): This study was conducted in 1 study center in Germany ([redacted]).

Publication Based on the Study: None

Study Period: Approximately 3 months

Study Initiation Date (Date of First Enrollment): Part A: 27 October 2011; Part B: 23 November 2011

Study Completion Date (Date of Last Evaluation): Part A: 20 January 2012; Part B: 03 February 2012

Phase of Development: Phase 1

Objectives:

The primary objectives of Part A were (1) to explore the effect of multiple doses of 100 mg ipragliflozin on the glucose homeostasis in fasted condition and after an oral glucose load in healthy subjects and patients with T2DM, (2) to assess the effect of multiple doses of 100 mg ipragliflozin on peripheral glucose utilization after an oral glucose load, (3) to assess the effect of multiple doses of 100 mg ipragliflozin on splanchnic glucose uptake after an oral glucose load, and (4) to assess the effect of multiple doses of 100 mg ipragliflozin on mean glucose levels in fasted condition and after an oral glucose load.

The primary objective of Part B was to assess (by administration of multiple doses of 12.5 or 100 mg ipragliflozin) the relationship between the exposure (AUC) to ipragliflozin in plasma, UGE and plasma glucose levels in patients with T2DM.

The secondary objectives of Part A were (1) to evaluate the effect of multiple doses of 100 mg ipragliflozin on steady state urinary sodium excretion (natriuresis), (2) to explore the effect of ipragliflozin on energy production and utilization of energy sources, (3) to evaluate the effect of multiple doses of 100 mg ipragliflozin on urinary glucose excretion (UGE), and (4) to evaluate the safety and tolerability of multiple doses of 100 mg ipragliflozin.

The secondary objective of Part B was to evaluate the safety and tolerability of multiple doses of 12.5 and 100 mg ipragliflozin in patients with T2DM.

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Methodology:

Part A was a randomized, double-blind, placebo-controlled, 2-period, 2-treatment, crossover study in healthy subjects and in T2DM patients who were drug-naïve or washed-out on metformin prior to admission to the clinical site. At a screening visit (day -41 to day -8 if subject was healthy or drug-naïve with T2DM, or day -41 to day -22 if patient with T2DM needed to be washed-out on metformin), inclusion and exclusion criteria were assessed and the subjects' eligibility verified. Subjects on a stable metformin treatment were washed-out (at least 3 weeks) prior to the first dose of study drug. Subjects were resident in the clinic for 2 periods of 9 days each, separated by a wash-out period of at least 2 weeks between the last dose of period 1 and the first dose of period 2. On day 1 (period 1), both the healthy subjects and T2DM patients were equally randomized to receive ipragliflozin and matching placebo in one of the following treatment orders: A) ipragliflozin 100 mg once daily for 6 days in period 1 and placebo to match ipragliflozin 100 mg once daily for 6 days in period 2 or B) placebo to match ipragliflozin 100 mg once daily for 6 days in period 1 and ipragliflozin 100 mg once daily for 6 days in period 2. An OGTT with double-tracer tracer methodology ([$^{13}C_6$]-glucose and [6,6-$^{2}H_2$]-glucose), plasma glucose and hormone measurements was performed at baseline (day -1) and after multiple dose administrations of ipragliflozin (day 6). Urine was collected from day -1 until day 7 in order to assess UGE and urine volume. Urinary sodium and creatinine excretion, as well as renal function parameters, were determined on day 5. Indirect calorimetry was performed in the morning on day -7 and on day 4. Serial blood samples for pharmacokinetic assessments over 24 hours were taken on day 6. Safety assessments comprised recording of adverse events throughout the study, clinical laboratory tests, vital sign measurements, electrocardiograms (ECGs) and physical examination. In the morning of day 7, after the last scheduled assessment, subjects were discharged from the clinic. An end of study visit took place 7-14 days after discharge of the second period.

Part B was an open-label, randomized, 2-period, 2-treatment, crossover study in T2DM patients who differed in their HbA1c levels (6.0% - 6.9%, 7.0% - 7.9%, 8.0% - 8.9% or 9.0% - 9.9%). At a screening visit, (day -21 to day -3), inclusion and exclusion criteria were assessed and the subjects' eligibility verified. Subjects were resident in the clinic for 2 periods of 8 days each, separated by a wash-out period of at least 5 days between the last dose of period 1 and the first dose of period 2. On day 1, the T2DM patients were equally randomized to receive ipragliflozin in one of the following treatment orders: A) 100 mg ipragliflozin once daily for 5 days in period 1 and 12.5 mg ipragliflozin once daily for 5 days in period 2 or B) 12.5 mg ipragliflozin once daily for 5 days in period 1 and 100 mg ipragliflozin once daily for 5 days in period 2. Urine was collected from day -1 until day 6 in order to assess UGE; plasma glucose was measured on day -1 and day 5. Serial blood samples for pharmacokinetic assessments over 24 hours were taken on day 5. Safety assessments comprised recording of adverse events throughout the study, clinical laboratory tests, vital sign measurements, ECGs, and physical examination. In the morning of day 6, after the last scheduled assessment, subjects were discharged from the clinic. An end of study visit took place 7 to 14 days after discharge of the second period.

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Number of Subjects (Planned, Enrolled and Analyzed):

For Part A, 12 healthy subjects and 12 patients with T2DM were planned to be included, with at least 4 of each gender in each group. Actually, 29 subjects were screened and 12 healthy subjects (6 men and 6 women) and 12 patients with T2DM (7 men and 5 women) were randomized and analyzed.

For Part B, 20 patients with T2DM were planned to be included (n = 5 having HbA1c in the range of 6.0% - 6.9%; n = 5 having HbA1c in the range of 7.0% - 7.9%; n = 5 having HbA1c in the range of 8.0% - 8.9%; n = 5 having HbA1c in the range of 9.0% - 9.9%). Actually, 32 subjects were screened and 20 (14 men and 6 women) were randomized and analyzed, with 5 patients in each HbA1c category.

Diagnosis and Main Criteria for Inclusion:

For Part A, subjects were eligible if they had signed the informed consent form prior to screening, were between 35 to 65 years (inclusive) of age, and had serum creatinine within the normal range. In addition, healthy subjects were required to be free of diabetes mellitus, with fasting plasma glucose (FPG) < 5.6 mmol/L and body mass index (BMI) ≥ 18.5 and < 28.0 kg/m^2. T2DM patients were required to have a diagnosis of T2DM for at least 6 months, a BMI ≥ 20.0 and < 35.0 kg/m^2, HbA1c > 7.0% and < 9.0%, and FPG < 10.0 mmol/L. Furthermore, T2DM patients had to be treatment naïve to glucose-lowering medication or to use metformin (to be washed out at least 3 weeks prior to the first dosing at day 1).

For Part B, subjects were eligible if they had signed the informed consent form prior to screening, were between 35 to 65 years (inclusive) of age, had a diagnosis of T2DM for at least 6 months, a BMI ≥ 20.0 and < 35.0 kg/m^2, HbA1c ≥ 6.0% and < 10.0%, and FPG < 10.0 mmol/L. Furthermore, the subjects had to be drug naïve or on a stable glucose lowering therapy (metformin, TZD, DPP-4 inhibitor or SUD therapy).

In both study parts, female subjects were required to be of non-child bearing potential; male subjects had to be non-fertile or to practice an adequate contraceptive method to prevent pregnancies.

Subjects were to be excluded from participation in the study if they met any of the exclusion criteria defined in the study protocol.

Test Product, Dose and Mode of Administration, Batch Numbers:

Tablets containing 50 mg ipragliflozin and 12.5 mg ipragliflozin were used during this study. In Part A, subjects received an oral dose of 100 mg ipragliflozin (2 tablets with 50 mg) in the morning of each treatment day (active treatment period). In Part B, subjects received an oral dose of 12.5 mg ipragliflozin (1 tablet with 12.5 mg) in the morning of each treatment day in one period and a respective dose of 100 mg (2 tablets with 50 mg) in the other period.

The batch numbers of the ipragliflozin tablets used in this study were: [redacted] (12.5 mg tablets) and [redacted] (50 mg tablets).

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Duration of Treatment (or Duration of Study, if applicable):

In Part A, treatment was administered for 6 days; in Part B, treatment was administered for 5 days.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Placebo tablets matched the 50 mg ASP1941 tablets. In Part A, 2 tablets were administered orally in the morning of each treatment day of the placebo period. In Part B, no placebo administration occurred.

The batch number of the placebo tablets was [redacted].

Criteria for Evaluation:

Part A, Pharmacokinetics

The following endpoints were determined for ipragliflozin and metabolite M2:

- AUC_{tau} (area under the plasma concentration time curve from dosing time to 24h postdose) on day 6
- C_{max} (maximum plasma concentration) on day 6
- t_{max} (time to maximum plasma concentration) on day 6
- CL/F (apparent total body clearance; i.e., dose/AUC_{tau}) on day 6 (ipragliflozin only)
- C_{trough} (plasma concentration at the end of dosing interval) on days 4, 5, 6, 7
- PTR (peak-trough ratio), i.e., C_{max} day 6 / C_{trough} day 7

Part A, Pharmacodynamics

The following endpoints related to glucose homoeostasis were determined during an OGTT on day -1 (baseline) and on day 6:

- $R_{a\ OGTT}$ AUC (AUC of the rate of glucose appearance from gut after OGTT) for intervals 0-1h, 0-2h, 0-4h, 0-6h
- EGP_{OGTT} AUC (AUC of the endogenous glucose production after OGTT) for intervals 0-1h, 0-2h, 0-4h, 0-6h
- $R_{a\ (total)}$ AUC (AUC of total glucose appearance = $R_{a\ OGTT}$ plus EGP_{OGTT}) for intervals 0-1h, 0-2h, 0-4h, 0-6h
- $R_{d\ OGTT}$ AUC (AUC of the rate of glucose disposal after OGTT) for intervals 0-1h, 0-2h, 0-4h, 0-6h
- Mean EGP_{basal} (mean endogenous glucose production in the time interval -1h to 0h before OGTT)
- Mean $R_{d\ basal}$ (mean rate of glucose disposal in the time interval -1h to 0h before OGTT)
- Mean $R_{d\ basal\ (corrected)}$ Intervals -2h to 0h (mean R_d basal in the time interval -2h to 0h before OGTT, corrected for UGE)

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- Mean UGE -2h to 0h (mean urinary glucose excretion in the time interval -2h to 0h before OGTT)
- Mean $R_{a\ OGTT}$ 0-6h (mean rate of glucose appearance in the time interval 0h to 6h after OGTT)
- Mean EGP_{OGTT} 0-6h (mean endogenous glucose production in the time interval 0h to 6h after OGTT)
- $\Delta EGP_{0\text{-}6h}$ (mean $EGP_{0\text{-}6h}$ after OGTT - mean EGP_{basal})
- Mean $R_{a\ (total)}$ 0-6h (mean total rate of glucose appearance in the time interval 0h to 6h after OGTT)
- Mean $R_{d\ OGTT}$ 0-6h (mean rate of glucose disposal in the time interval 0h to 6h after OGTT)
- Mean $R_{d\ OGTT\ (corrected)}$ Intervals 0h to 6h (mean $R_{d\ OGTT}$ in the time interval 0h to 6h after OGTT, corrected for UGE)
- Mean UGE 0h to 6h (mean urinary glucose excretion in the time interval 0h to 6h before OGTT)
- Glucose bioavailability = [total $R_{a\ OGTT}$]/[total glucose in OGTT] x 100%
- Glucose AUC (area under the plasma glucose concentration time curve) for intervals -2-0h before and 0-1h, 0-2h, 0-3h, 0-4h and 0-6h after OGTT
- Glucose C_{max} (maximum plasma glucose concentration in the time interval 0-6h after OGTT
- Insulin AUC for intervals 0-1h before and 0-2h, 0-3h and 0-4h after OGTT
- Insulin C_{max} (maximum plasma insulin concentration in the time interval 0-6h after OGTT)
- Glucagon AUC for intervals 0-1h before and 0-2h and 0-4h after OGTT
- Glucagon C_{max} (maximum plasma glucagon concentration in the time interval 0-6h after OGTT)
- GLP-1 AUC for intervals 0-1h, 0-2h and 0-4h after OGTT
- GLP-1 C_{max} (maximum plasma GLP-1 concentration in the time interval 0-6h after OGTT)
- PYY 3-36 AUC for intervals 0-1h, 0-2h and 0-4h after OGTT
- PYY 3-36 C_{max} (maximum plasma PYY 3-36 concentration in the time interval 0-6h after OGTT)
- GIP AUCs for intervals 0-1h, 0-2h and 0-4h after OGTT
- GIP C_{max} (maximum plasma GIP concentration in the time interval 0-6h after OGTT)

Furthermore, the following endpoints were determined:

- $UGE_{0\text{-}24}$ (24-hour postdose urinary glucose excretion) from day -1 through day 6
- 24-hour postdose urine volume from day -1 through day 6
- $Ae_{0\text{-}24h(Na)}$ (24-hour postdose urinary sodium excretion) on day 5

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- $Ae_{0\text{-}24h(Cr)}$ (24-hour postdose urinary creatinine excretion) on day 5
- $Ae_{0\text{-}2h(Glu)}$ (amount of glucose excreted via urine in the interval 0-2h postdose) on day -1 and on day 6
- $Ae_{2\text{-}6h(Glu)}$ (amount of glucose excreted via urine in the interval 2-6h postdose) on day -1 and on day 6
- $Ae_{0\text{-}6h(Glu)}$ ((amount of glucose excreted via urine in the interval 0-6h postdose) on day -1 and on day 6
- Sodium in blood (serum) on day 5
- Creatinine in blood (serum) on day 5
- CL_{Cr} (creatinine clearance) on day 5
- eGFR (estimated glomerular filtration rate) at screening, on day -2, day -1 and day 5
- Cystatin C in serum on day -2 and day 5

The following endpoints regarding energy production and substrate utilization were determined on day -7 (baseline) and on day 4:

- RMR (resting metabolic rate)
- V_{O2} (oxygen consumption)
- V_{CO2} (carbon dioxide production)
- RER (respiratory exchange ratio)
- CHO (carbohydrate oxidation rate)
- FAT (lipid oxidation rate)

Part A, Safety

- Adverse events
- Safety laboratory tests (hematology, biochemistry, urinalysis)
- Vital signs (systolic and diastolic blood pressure, pulse)
- 12-lead ECG
- Physical examination

Part B, Pharmacokinetics

The following endpoints were determined for ipragliflozin and metabolite M2:

- AUC_{tau} (area under the plasma concentration time curve from dosing time to 24h postdose) on day 5
- C_{max} (maximum plasma concentration) on day 5

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- t_{max} (time to maximum plasma concentration) on day 5
- CL/F (apparent total body clearance; i.e., dose/AUC_{tau}) on day 5 (ipragliflozin only)
- C_{trough} (plasma concentration at the end of dosing interval) on days 3, 4, 5, 6
- PTR (peak-trough ratio); i.e., C_{max} day 5 / C_{trough} day 6

Part B, Pharmacodynamics

- UGE_{0-24} (24-hour postdose urinary glucose excretion) from day -1 through day 5
- $C_{average}$ (average concentration) of plasma glucose on day -1 and on day 5
- Plasma glucose AUC_{0-24h} (area under the plasma glucose concentration time curve for the interval 0-24h postdose) on day -1 and on day 5

Part B, Safety

- Adverse events
- Safety laboratory tests (hematology, biochemistry, urinalysis)
- Vital signs (systolic and diastolic blood pressure, pulse)
- 12-lead ECG
- Physical examination

Statistical Methods:

All data processing, summarization, and analyses were performed using SAS® Version 9.2 in a PC environment. The descriptive statistical analyses of the data and the inferential statistical analyses were performed by [redacted], Germany.

The following analysis sets were used: The Safety Analysis Set (SAF) consisted of all those subjects who were randomized to receive study treatment and who received at least 1 dose of study medication, regardless of whether or not they subsequently completed the study and whether or not they deviated from the protocol or were later found to have violated the study's inclusion or exclusion criteria. The Pharmacokinetic Analysis Set (PKAS) consisted of all those subjects in the SAF who had at least one evaluable set of drug concentration data. The Pharmacodynamic Analysis Set (PDAS) consisted of all those subjects in the SAF who had at least one evaluable set of blood glucose or insulin data after dosing.

For Part A, statistical analyses were performed on pharmacodynamic variables only. As part of the assessment of model validity, the distributional properties of the dependent variables were examined. Analyses of normally distributed data were performed parametrically based on a linear mixed model using a parameterization appropriate for a 2-period, 2-treatment, crossover design.

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The within-group change in the defined parameters of ipragliflozin compared to placebo was analyzed with a linear mixed model using the difference of the post-dose and baseline data as response variable, treatment, period, sequence and subject group (healthy or T2DM) as fixed effect, baseline data as covariate, subject within sequence as random effect, and treatment*subject group as interaction term. The difference between T2DM patients and healthy subjects in the change in the defined parameters was analyzed with a linear mixed model using the post-dose difference of ipragliflozin and placebo minus the baseline difference of ipragliflozin and placebo as response variable, subject group (healthy or T2DM) and sequence as fixed effect, and the baseline difference as covariate. Within each model, least square means per treatment were calculated and the least square means and the difference of least square means (ipragliflozin - placebo) were shown with a P-value and a 95% confidence interval.

In some instances, within- and between-group comparisons were not performed on the change from baseline but on the day 5 results (e.g., $Ae_{0\text{-}24h(Na)}$, $Ae_{0\text{-}24h(Cr)}$, sodium and creatinine in serum).

In cases where data were not normally distributed and a log transformation was also deemed unsuccessful in normalizing the data, a nonparametric technique using Wilcoxon's signed rank test was employed. The estimate of Hodges and Lehmann and the corresponding 95% nonparametric confidence interval was shown with the median difference and a P-value. In the cases where such a nonparametric analysis was chosen based on the model checking assumptions, an additional parametric approach was also calculated. This was justified by the fact that due to the small sample sizes a totally reliable assessment of the data distribution could not be guaranteed.

As the study may not be properly powered, reliance on the significance or otherwise of P-value is considered inappropriate. Therefore, interpretation of statistical analysis results is predominantly based on estimates and respective confidence intervals.

In addition to the analyses described above, descriptive statistics were also provided for all pharmacodynamic variables. Renal function parameters (CL_{Cr}, eGFR, Cystatin C, determined on day 5), as well as pharmacokinetic and safety assessments, were solely evaluated by means of descriptive statistics.

For Part B, all analyses (pharmacodynamic, pharmacokinetic and safety) were performed by descriptive methods only.

The coding dictionary for this study was the Medical Dictionary for Regulatory Activities (MedDRA), Version 12.1.

Summary of Results/Conclusions:

Population:

In Part A, 29 subjects were screened of which 5 were screening failures and 24 subjects (12 healthy and 12 with T2DM) were randomized. Six subjects in each group were randomized to treatment with ipragliflozin followed

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by matching placebo (Sequence AB) while the other 6 subjects received treatment in the reverse order; i.e., placebo first and then ipragliflozin (Sequence BA). All 24 randomized subjects were included in the safety analysis set as well as in the pharmacodynamic and the pharmacokinetic analysis set, and all subjects completed the study. The healthy subject population consisted of 6 men (50.0%) and 6 women (50.0%) and the T2DM population of 7 men (58.3%) and 5 women (41.7%), with the following demographic and baseline characteristics:

Table 1 Part A: Summary Statistics of Demographic and Baseline Characteristics (SAF)

Parameter (Unit)	Subject Group	Mean	SD	Median	Min	Max
Age (years)	Healthy	46.1	8.69	46.0	36	63
	T2DM	59.0	6.16	61.5	43	64
Weight (kg)	Healthy	73.78	13.472	71.40	56.3	101.0
	T2DM	84.53	10.340	85.75	70.7	102.5
Height (cm)	Healthy	172.6	11.07	169.5	160	190
	T2DM	168.7	8.81	167.0	159	186
BMI (kg/m^2)	Healthy	24.55	1.669	24.55	21.8	28.0
	T2DM	29.75	3.374	29.55	24.4	34.8
FPG (mmol/L)	Healthy	4.917	0.4743	5.030	3.78	5.50
	T2DM	8.461	0.5430	8.480	7.45	9.45
HbA1c (%)	Healthy	5.53	0.234	5.55	5.1	5.8
	T2DM	7.67	0.477	7.60	7.1	8.9
eGFR ($mL/min/1.73\ m^2$)	Healthy	103.90	16.066	102.75	79.7	124.5
	T2DM	93.89	15.041	98.45	67.9	112.2
Systolic blood pressure (mmHg)	Healthy	118.5	6.01	119.0	109	126
	T2DM	139.3	12.69	137.0	119	158
Diastolic blood pressure (mmHg)	Healthy	75.3	6.41	75.0	65	88
	T2DM	86.2	9.01	86.0	73	98
Pulse (beats/ min)	Healthy	62.7	9.44	62.0	51	80
	T2DM	70.0	8.80	68.0	60	85

All subjects who were randomized to receive study treatment and who received at least 1 dose of study medication (Safety Analysis Set, SAF); n = 12 for each subject group.

BMI: body mass index; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate; Min: minimum; Max: maximum; SD: standard deviation; T2DM: type 2 diabetes mellitus.

Source: Table 12.1.2.1

In Part B, 32 subjects were screened of which 12 were screening failures and 20 subjects (all with T2DM, 5 in each of the 4 HbA1c categories) were randomized. Ten patients were randomized to treatment with ipragliflozin 100 mg followed by 12.5 mg (Sequence AB) while the other 10 patients received treatment in the reverse order; i.e., 12.5 mg first and then 100 mg (Sequence BA). All 20 randomized patients were included in the safety analysis sets as well as in the pharmacodynamic and the pharmacokinetic analysis sets, and all patients completed the study.

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The population of Part B consisted of 14 men (70.0%) and 6 women (30.0%) with T2DM and with the following demographic and baseline characteristics:

Table 2 Part B: Summary Statistics of Demographic and Baseline Characteristics (SAF)

Parameter (Unit)	Mean	SD	Median	Min	Max
Age (years)	56.6	5.59	58.0	43	65
Weight (kg)	88.08	13.339	88.10	61.5	109.0
Height (cm)	174.3	9.91	175.0	149	193
BMI (kg/m^2)	29.03	3.900	29.15	20.5	34.8
FPG (mmol/L)	8.470	1.3066	8.725	5.78	10.68
HbA1c (%)	7.86	1.165	7.85	6.0	9.9
eGFR (mL/min/1.73 m^2)	100.37	21.945	99.50	68.5	144.9
Systolic blood pressure (mmHg)	139.4	12.96	142.0	114	160
Diastolic blood pressure (mmHg)	84.2	5.71	85.0	70	92
Pulse (beats/ min)	67.8	9.29	67.0	50	88

All subjects who were randomized to receive study treatment and who received at least 1 dose of study medication (Safety Analysis Set, SAF); n = 20.

BMI: body mass index; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate; Min: minimum; Max: maximum; SD: standard deviation.

Source: Table 12.1.2.1

Pharmacokinetic Results Part A:

Part A pharmacokinetic results for ipragliflozin and metabolite M2 are summarized in Table 3

Table 3 Part A: Summary of Ipragliflozin and Metabolite M2 Pharmacokinetic Parameters in Healthy Subjects and Patients With T2DM on Day 6 of Repeated Dosing of 100 mg Once Daily 6 Days (PKAS)

Parameter (Unit)	Analyte	Healthy Subjects			T2DM Patients		
		n	Mean	SD	n	Mean	SD
AUC_{tau} (ng·h/mL)	Ipra	12	8067.461	1781.073	12	8151.884	1832.601
	M2	12	5427.269	1232.186	12	7117.445	2299.769
C_{max} (ng/mL)	Ipra	12	1502.426	276.5702	12	1711.133	456.3107
	M2	12	958.658	219.6752	12	1228.204	383.1437
t_{max} (h)	Ipra	12	1.571	0.5875	12	1.119	0.3631
	M2	12	2.054	0.7377	12	1.706	0.3687
CL/F (L/h)	Ipra	12	12.968	2.8866	12	12.810	2.8028
	M2	12	NA	NA	12	NA	NA
PTR (--)	Ipra	12	18.204	7.6543	12	19.918	6.9361
	M2	12	18.357	9.0477	12	17.080	5.6186
C_{trough} day 4 (ng/mL)	Ipra	12	84.478	25.9546	12	94.345	34.6953
	M2	12	52.285	16.1996	12	79.708	38.7704
C_{trough} day 5 (ng/mL)	Ipra	12	88.279	27.8101	12	99.688	38.2174
	M2	12	52.293	19.4820	12	85.593	40.9788

Table continued on next page

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Table 3 continued

C_{trough} day 6 (ng/mL)	Ipra	12	86.950	23.7135	12	95.143	41.9425
	M2	12	55.576	17.0039	12	76.824	41.3275
C_{trough} day 7 (ng/mL)	Ipra	12	91.438	32.2631	12	94.162	38.6332
	M2	12	59.938	22.5558	12	77.001	33.5751

All subjects in the Safety Analysis Set (SAF) who had at least one evaluable set of drug concentration data (Pharmacokinetic Analysis Set [PKAS]).

One value below limit of quantification has been set to missing and linear interpolated (Subject no. [redacted]).

All pharmacokinetic parameters were determined on day 6; C_{trough} was also determined on days 4, 5 and 7.

(--): no units; CV %: coefficient of variation, expressed in percent; Min: minimum; Max: maximum; NA: not applicable; PTR: peak-trough ratio; SD: standard deviation.

Source: Tables 12.4.1.2 and 12.4.2.2

Ipragliflozin: Mean AUC_{tau} on day 6 was similar in healthy subjects and patients with T2DM (8067 and 8152 ng·h/mL). Mean C_{max} was higher in the T2DM patients than in the healthy subjects group (1711 vs 1502 ng/mL), and the mean time until C_{max} (t_{max}) was shorter (1.1 vs 1.6 h). Mean apparent total body clearance (CL/F) was similar for both groups (13 L/h). Mean peak-trough ratio (PTR) was 20 in the T2DM patients and 18 in the healthy subjects group. Mean trough concentrations on days 4, 5, 6 and 7 did not show any relevant further increase. However, mean C_{trough} in the T2DM group was on each day slightly higher than in the healthy subjects group.

Metabolite M2: Mean AUC_{tau} on day 6 was larger in patients with T2DM than in healthy subjects (7117 vs 5427 ng·h/mL). The same applied to mean C_{max} (1228 vs 959 ng/mL), and the mean time until C_{max} (t_{max}) was shorter (1.7 vs 2.1 h). Mean peak-trough ratio (PTR) was 17 in the T2DM patients and 18 in the healthy subjects group. Mean trough concentrations on days 4, 5, 6 and 7 did not show any relevant further increase. However, mean C_{trough} in the T2DM group was on each day higher than in the healthy subjects group. CV% of C_{trough} was larger in T2DM patients than in healthy subjects, suggesting higher variability of C_{trough} values in T2DM patients.

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Pharmacokinetic Results Part B:

Part B pharmacokinetic results for ipragliflozin and metabolite M2 are summarized in Table 4

Table 4 Part B: Summary Statistics of Ipragliflozin Pharmacokinetic Parameters in Patients With T2DM on Day 5 of Repeated Dosing of 12.5 and 100 mg Once Daily (PKAS)

Parameter (Unit)	Analyte	Ipragliflozin 12.5 mg			Ipragliflozin 100 mg		
		n	Mean	SD	n	Mean	SD
AUC_{tau} (ng·h/mL)	Ipra	20	883.047	271.7273	20	6904.304	1646.428
	M2	20	652.693	354.7001	20	5086.589	1850.000
C_{max} (ng/mL)	Ipra	20	191.574	123.6134	20	1263.139	334.3571
	M2	20	126.973	142.6187	20	789.885	314.5252
t_{max} (h)	Ipra	20	2.047	0.8942	20	2.098	0.8167
	M2	20	2.913	0.9073	20	2.962	0.9786
CL/F (L/h)	Ipra	20	15.254	4.2063	20	15.209	3.3471
	M2	20	NA	NA	20	NA	NA
PTR (--)	Ipra	20	18.986	10.4267	20	16.155	7.8968
	M2	20	15.424	7.7231	20	12.913	5.5449
C_{trough} day 3 (ng/mL)	Ipra	20	9.393	3.3184	20	84.047	33.2414
	M2	20	6.659	2.6120	20	58.611	23.9120
C_{trough} day 4 (ng/mL)	Ipra	20	10.344	3.3794	20	91.994	32.5238
	M2	20	6.944	2.5938	20	64.671	28.2141
C_{trough} day 5 (ng/mL)	Ipra	20	10.748	3.8843	20	93.466	43.2291
	M2	20	7.124	2.6202	20	64.171	29.9313
C_{trough} day 6 (ng/mL)	Ipra	20	10.559	3.4298	20	90.860	39.6466
	M2	20	7.891	3.3259	20	70.496	37.4570

All subjects in the Safety Analysis Set (SAF) who had at least one evaluable set of drug concentration data (Pharmacokinetic Analysis Set [PKAS]).

All pharmacokinetic parameters were determined on day 5; C_{trough} was also determined on days 3, 4 and 6.

(--): no units; CV %: coefficient of variation, expressed in percent; Ipra: ipragliflozin; Min: minimum; Max: maximum; NA not applicable; PTR: peak-trough ratio; T2DM: type 2 diabetes mellitus; SD: standard deviation.

Source: Tables 12.4.1.2 and 12.4.2.2

Ipragliflozin: Mean AUC_{tau} on day 5 was larger after 100 mg than after 12.5 mg ipragliflozin (6904 vs 883 ng/mL) in the T2DM patients, who constituted the population of this study part. Correspondingly, mean C_{max} was higher (1263 vs 192 ng/mL). Mean time until C_{max} (t_{max}) was similar (2.1 and 2.0 h), as well as the mean apparent total body clearance (CL/F) (15 L/h at both dose levels). Mean peak-trough ratio (PTR) was 19 for the 12.5 mg and 16 for the 100 mg dose. At both doses, mean trough concentrations showed a slight increase between day 3 and day 4 and remained then fairly constant on days 4, 5 and 6. Mean C_{trough} was higher for the 100 mg than for the 12.5 mg dose.

Metabolite M2: Mean AUC_{tau} on day 5 of metabolite M2 was larger after 100 mg than after 12.5 mg ipragliflozin (5087 vs 653 ng/mL) in the T2DM patients, who constituted the population of this study part. Correspondingly, mean C_{max} was higher (790 vs 127 ng/mL) while the mean time until C_{max} (t_{max}) was similar

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(3.0 and 2.9 h). Mean peak-trough ratio (PTR) was 15 for the 12.5 mg and 13 for the 100 mg dose. At both doses, mean trough concentrations showed a slight increase between day 3 and day 6. Mean C_{trough} was higher for the 100 mg than for the 12.5 mg dose.

Pharmacodynamic Results Part A:

OGTT – Tracer Results

Table 5 summarizes the results of the tracer measurements for healthy subjects and patients with T2DM.

Table 5 **Summary Statistics of Basal and OGTT Tracer Parameters and UGE in Healthy Subjects and T2DM Patients at Baseline and on Day 6 of Repeated Dosing of 100 mg Once Daily Ipragliflozin or Placebo (PDAS)**

Parameter (Unit)	Treatment	Day/ Change †	Healthy Subjects			T2DM Patients		
			n	Mean	SD	n	Mean	SD
$R_{a\ OGTT}$ AUC_{0-6h} (mcmol/kg)	Ipragliflozin	-1	11	6427.109	1216.343	12	5887.069	700.6158
		6	12	6276.899	997.1691	11	5882.363	864.0986
		Change	11	-4.966	504.7091	11	-29.916	456.7820
	Placebo	-1	12	6494.044	1017.029	12	5843.847	725.1058
		6	12	6533.847	960.3428	12	5898.796	652.0230
		Change	12	39.803	652.4594	12	54.949	448.1403
EGP_{OGTT} AUC_{0-6h} (mcmol/kg)	Ipragliflozin	-1	11	2085.238	570.9848	12	1210.148	272.1861
		6	12	2151.931	420.0772	12	1490.766	187.6572
		Change	11	63.818	502.0456	12	280.618	281.1152
	Placebo	-1	12	2013.615	596.2034	12	1247.416	365.5317
		6	12	1805.823	365.9411	12	1105.926	164.9460
		Change	12	-207.792	499.0990	12	-141.491	237.6684
$R_{a\ (total)}$ AUC_{0-6h} (mcmol/kg)	Ipragliflozin	-1	11	8512.347	1375.897	12	7097.217	772.1044
		6	12	8428.830	1052.870	11	7386.312	871.7544
		Change	11	58.853	837.4770	11	235.183	486.5145
	Placebo	-1	12	8507.659	1295.156	12	7091.263	884.1396
		6	12	8339.670	1130.483	12	7004.721	749.6777
		Change	12	-167.989	795.3462	12	-86.542	449.9986
$R_{d\ OGTT}$ AUC_{0-6h} (mcmol/kg)	Ipragliflozin	-1	12	8265.869	1468.352	12	7107.838	771.4942
		6	12	8296.661	1152.463	12	7384.981	816.2420
		Change	12	30.792	916.7462	12	277.142	596.1158
	Placebo	-1	11	8204.596	1244.860	12	7050.609	1035.330
		6	12	8125.773	1019.402	12	6906.839	828.1916
		Change	11	-119.360	863.5281	12	-143.770	490.6035
Mean EGP_{basal} (mcmol/min/kg)	Ipragliflozin	-1	11	11.915	1.4675	12	12.561	1.3735
		6	12	12.552	1.3619	12	13.470	1.1908
		Change	11	0.677	1.5475	12	0.909	1.4035
	Placebo	-1	12	11.217	0.9840	12	12.658	1.6271
		6	12	11.069	1.0341	12	12.461	1.6687
		Change	12	-0.148	0.6088	12	-0.198	1.4164

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Table 5 continued

Parameter (Unit)	Treatment	Day/ Change †	Healthy Subjects			T2DM Patients		
			n	Mean	SD	n	Mean	SD
Mean $R_{d\ basal}$ (mcmol/min/kg)	Ipragliflozin	-1	12	12.099	1.4918	12	12.894	1.3735
		6	12	12.885	1.3619	12	13.803	1.1908
		Change	12	0.786	1.5231	12	0.909	1.4036
	Placebo	-1	11	11.468	0.9884	12	12.991	1.6271
		6	12	11.402	1.0341	12	12.794	1.6687
		Change	11	-0.082	0.5923	12	-0.198	1.4164
Mean $R_{d\ basal\ (corrected)}$ Intervals -2h to 0h (mcmol/min/kg)	Ipragliflozin	-1	12	12.093	1.4928	12	12.862	1.3747
		6	12	11.004	1.1010	12	10.009	1.2461
		Change	12	-1.090	1.0244	12	-2.853	1.5297
	Placebo	-1	12	11.546	0.9831	12	12.869	1.4545
		6	12	11.395	1.0369	12	12.670	1.5599
		Change	12	-0.150	0.6132	12	-0.199	1.4168
Mean UGE -2h to 0h (mcmol/min/kg)	Ipragliflozin	-1	12	0.006	0.0038	12	0.032	0.0736
		6	12	1.870	0.7844	12	3.716	1.2387
		Change	-	ND	ND	-	ND	ND
	Placebo	-1	12	0.005	0.0031	12	0.120	0.3606
		6	12	0.007	0.0061	12	0.119	0.3589
		Change	-	ND	ND	-	ND	ND
Mean $R_{a\ OGTT}$ 0-6h (mcmol/min/kg)	Ipragliflozin	-1	11	17.853	3.3787	12	16.353	1.9462
		6	12	17.436	2.7699	11	16.340	2.4003
		Change	11	-0.014	1.4020	11	-0.083	1.2688
	Placebo	-1	12	18.039	2.8251	12	16.233	2.0142
		6	12	18.150	2.6676	12	16.386	1.8112
		Change	12	0.111	1.8124	12	0.153	1.2448
Mean EGP_{OGTT} 0-6h (mcmol/min/kg)	Ipragliflozin	-1	11	5.792	1.5861	12	3.362	0.7561
		6	12	5.978	1.1669	12	4.141	0.5213
		Change	11	0.177	1.3946	12	0.779	0.7809
	Placebo	-1	12	5.593	1.6561	12	3.465	1.0154
		6	12	5.016	1.0165	12	3.072	0.4582
		Change	12	-0.577	1.3864	12	-0.393	0.6602

Table continued on next page

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Table 5 continued

Parameter (Unit)	Treatment	Day/ Change †	Healthy Subjects			T2DM Patients		
			n	Mean	SD	n	Mean	SD
$\Delta EGP_{0\text{-}6h}$ (mcmol/min/kg)	Ipragliflozin	-1	11	-6.123	1.2584	12	-9.199	1.5638
		6	12	-6.574	1.2253	12	-9.329	1.1145
		Change	11	-0.500	1.1092	12	-0.130	1.3450
	Placebo	-1	12	-5.624	1.4130	12	-9.193	1.3375
		6	12	-6.053	1.1327	12	-9.389	1.6179
		Change	12	-0.430	1.3978	12	-0.195	1.2675
Mean $R_{a\ (total)}$ 0-6h (mcmol/min/kg)	Ipragliflozin	-1	11	23.645	3.8219	12	19.714	2.1447
		6	12	23.413	2.9246	11	20.518	2.4215
		Change	11	0.163	2.3263	11	0.653	1.3514
	Placebo	-1	12	23.632	3.5977	12	19.698	2.4559
		6	12	23.166	3.1402	12	19.458	2.0824
		Change	12	-0.467	2.2093	12	-0.240	1.2500
Mean $R_{d\ OGTT}$ 0-6h (mcmol/min/kg)	Ipragliflozin	-1	12	22.961	4.0788	12	19.744	2.1430
		6	12	23.046	3.2013	12	20.514	2.2673
		Change	12	0.086	2.5465	12	0.770	1.6559
	Placebo	-1	11	22.791	3.4579	12	19.585	2.8759
		6	12	22.572	2.8317	12	19.186	2.3005
		Change	11	-0.332	2.3987	12	-0.399	1.3628
Mean $R_{d\ OGTT\ (corrected)}$ Intervals 0h to 6h (mcmol/min/kg)	Ipragliflozin	-1	12	22.935	4.0851	12	18.143	2.1405
		6	12	19.747	3.5039	12	14.469	2.9091
		Change	12	-3.189	2.5543	12	-3.674	1.6956
	Placebo	-1	11	22.771	3.4663	12	17.915	2.6139
		6	12	22.535	2.8439	12	17.543	2.3006
		Change	11	-0.352	2.3920	12	-0.372	1.1542
Mean UGE 0h to 6h (mcmol/min/kg)	Ipragliflozin	-1	12	0.025	0.0618	12	1.601	1.1375
		6	12	3.299	0.9480	12	6.045	1.5923
		Change	-	ND	ND	-	ND	ND
	Placebo	-1	12	0.018	0.0347	12	1.670	1.5586
		6	12	0.037	0.0872	12	1.642	1.4768
		Change	-	ND	ND	-	ND	ND
Glucose bioavailability (%)	Ipragliflozin	-1	11	102.764	7.3062	12	105.833	6.4148
		6	12	100.350	5.8429	12	105.592	9.3590
		Change	11	-2.755	9.9081	12	-0.242	10.4553
	Placebo	-1	12	105.167	6.0623	12	103.825	5.2295
		6	12	103.517	6.9489	12	105.792	4.9665
		Change	12	-1.650	9.2319	12	1.967	6.7395

All subjects in the Safety Analysis Set (SAF) who had at least one evaluable set of blood glucose or insulin data after dosing (Pharmacodynamic Analysis Set [PDAS]). In some cases data from subjects were excluded due to implausible values.

Bioavailability = [Total Ra OGTT]/[Total Glucose in OGTT] x 100%.

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Table 5 footnote continued

-: not applicable; EGP: endogenous glucose production; Min: minimum; Max: maximum; ND: not determined; OGTT: oral glucose tolerance test; Ra: rate of glucose appearance from gut; Rd: rate of glucose disposal; SD: standard deviation; UGE: urinary glucose excretion.

† Change from baseline (i.e., day 6 result minus day -1 result)

Source: Tables 12.5.1.2, 12.5.1.6, 12.5.1.10, 12.5.2.2, 12.5.2.6, 12.5.2.11, 12.5.2.14, 12.5.2.19, 12.5.2.22.1, 12.5.2.22.2, 12.5.2.22.3, 12.5.2.22.4, 12.2.22.5, 12.5.2.23, 12.5.3.1 and 12.5.5.3

Both in healthy subjects and in patients with T2DM, mean EGP_{basal} and mean $R_{d\ basal}$ increased, compared to placebo, from day -1 to day 6 with ipragliflozin (95% CIs of LS-mean difference ipragliflozin – placebo above zero). However, no difference between the subject groups could be shown with respect to the baseline-adjusted response (ipragliflozin – placebo).

Mean $R_{d\ basal\ (corrected)}$ -2 h to 0h decreased, compared to placebo, from day -1 to day 6 with ipragliflozin, but only in the T2DM group a difference between the treatments could be demonstrated (95% CI of LS-mean difference ipragliflozin – placebo below zero). Furthermore, a difference between the subject groups was indicated statistically (95% CI of LS-mean difference healthy – T2DM above zero) with respect to the baseline-adjusted response (ipragliflozin – placebo).

Both in healthy subjects and in patients with T2DM, EGP decreased after OGTT, compared to basal EGP. The decrease was, however, less with ipragliflozin than with placebo. This is reflected by an increase in the respective EGP_{OGTT} AUCs, compared to placebo, from day 1 to day 6 with ipragliflozin, but 95% CIs of LS-mean difference ipragliflozin – placebo are above zero only for the intervals 0-1h (healthy and T2DM patients), 0-4h (healthy subjects only), and 0 6h (healthy and T2DM patients). No difference between the subject groups was evident with respect to the baseline-adjusted response (ipragliflozin – placebo).

Both in healthy and T2DM patients, mean $R_{d\ OGTT\ (corrected)}$ in the time interval 0 to 6 h decreased, compared to placebo, from day -1 to day 6 with ipragliflozin (95% CIs of LS-mean difference ipragliflozin – placebo below zero). No difference between the subject groups could be shown with respect to the baseline-adjusted response (ipragliflozin – placebo).

Neither for healthy subjects nor for patients with T2DM could a change in $\Delta EGP_{0\ 6h}$, glucose bioavailability and $R_{a\ OGTT}$, $R_{a\ (total)}$ and $R_{d\ OGTT}$ AUCs be demonstrated statistically, and there were no differences between the subject groups. Although no change in $R_{d\ OGTT}$ AUCs could be statistically demonstrated, the changes point towards an increased R_d (with high variability) under ipragliflozin treatment in T2DM patients since all 95% CIs include zero but all are somewhat skewed to the right.

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OGTT – Plasma Glucose and Hormone Results

Table 6 summarizes the results of the plasma glucose and hormone measurements for healthy subjects and patients with T2DM.

Table 6 Summary Statistics of OGTT Plasma Glucose and Hormones in Healthy Subjects and T2DM Patients at Baseline and on Day 6 of Repeated Dosing of 100 mg Once Daily Ipragliflozin or Placebo (PDAS)

Parameter (Unit)	Treatment	Day/ Change †	Healthy Subjects		T2DM Patients	
			Mean	SD	Mean	SD
Glucose AUC_{0-6h} (h·mmol/L)	Ipragliflozin	-1	34.658	2.7799	85.743	14.2583
		6	35.609	2.7893	66.615	9.8200
		Change	0.951	2.7858	-19.128	10.4942
	Placebo	-1	33.963	2.6508	83.265	16.3285
		6	37.272	1.9950	87.091	18.1539
		Change	3.309	1.7074	3.826	6.2645
Glucose AUC_{0-4h} (h·mmol/L)	Ipragliflozin	-1	25.864	2.8487	65.948	9.5103
		6	26.672	2.3873	53.093	7.1067
		Change	0.809	2.2856	-12.855	7.3019
	Placebo	-1	25.141	2.6876	63.782	10.4024
		6	28.266	2.3103	66.643	12.0900
		Change	3.125	1.6458	2.861	4.4414
Glucose C_{max} (mmol/L)	Ipragliflozin	-1	9.631	1.6302	21.455	2.8944
		6	9.774	1.1335	18.147	2.1906
		Change	0.143	1.4820	-3.307	2.4796
	Placebo	-1	9.034	0.9768	20.335	2.8005
		6	10.690	1.7167	21.103	3.5756
		Change	1.656	1.3920	0.768	1.9281

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Table 6 continued

Parameter (Unit)	Treatment	Day/ Change †	Healthy Subjects		T2DM Patients	
			Mean	SD	Mean	SD
Insulin AUC_{0-4h} (h·mU/L)	Ipragliflozin	-1	126.769	56.6162	127.979	66.9951
		6	117.738	39.7512	109.879	63.4342
		Change	-9.031	28.5714	-18.100	21.7353
	Placebo	-1	129.147	62.5538	134.598	81.2950
		6	124.919	45.7213	121.383	72.3668
		Change	-4.228	46.7304	-13.215	28.3605
Insulin C_{max} (mU/L)	Ipragliflozin	-1	66.875	42.2109	48.775	24.6892
		6	60.658	25.5050	42.142	25.9362
		Change	-6.217	21.9510	-6.633	11.4250
	Placebo	-1	72.600	35.8814	53.300	39.6044
		6	61.342	22.6948	42.000	23.7037
		Change	-11.258	27.3500	-11.300	27.4411
Glucagon AUC_{0-4h} (h·pmol/L)	Ipragliflozin	-1	205.102	31.5391	225.023	27.1675
		6	200.452	30.0126	237.400	39.1368
		Change	-4.650	12.0150	12.377	20.7262
	Placebo	-1	202.682	26.3793	219.292	29.6830
		6	190.960	28.4125	212.800	29.9124
		Change	-11.722	11.9368	-6.491	15.0659
Glucagon C_{max} (pmol/L)	Ipragliflozin	-1	62.175	18.3971	67.442	15.3506
		6	62.758	17.0584	73.442	18.5190
		Change	0.583	6.0806	6.000	7.4072
	Placebo	-1	62.733	18.3957	62.908	10.7839
		6	57.133	12.0555	63.475	13.0902
		Change	-5.600	10.0287	0.567	6.2948
GLP-1 AUC_{0-4h} (h·pmol/L)	Ipragliflozin	-1	28.479	11.4327	34.581	35.3792
		6	23.527	11.1704	31.094	32.3134
		Change	-4.952	9.8061	-3.488	11.2242
	Placebo	-1	28.507	11.7935	37.300	39.0855
		6	24.521	12.1594	33.078	37.9447
		Change	-3.987	9.6216	-4.222	14.3698
GLP-1 C_{max} (pmol/L)	Ipragliflozin	-1	13.717	10.6293	16.183	13.0130
		6	9.533	4.9950	14.358	11.3711
		Change	-4.183	9.8850	-1.825	9.0350
	Placebo	-1	16.967	12.4939	15.583	12.8485
		6	9.725	6.6650	14.525	14.9032
		Change	-7.242	13.1245	-1.058	13.8529
PYY 3-36 AUC_{0-4h} (h·ng/L) ‡	Ipragliflozin	-1	185.254	80.1862	171.715	86.6434
		6	191.057	63.6872	193.099	62.6379
		Change	5.803	36.8272	21.384	55.2939
	Placebo	-1	195.299	64.5505	185.499	81.3908
		6	181.492	65.4164	184.455	92.7086
		Change	-13.808	45.2499	-1.044	66.2406

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Table 6 continued

Parameter (Unit)	Treatment	Day/ Change †	Healthy Subjects		T2DM Patients	
			Mean	SD	Mean	SD
PYY 3-36 C_{max} (ng/L) ‡	Ipragliflozin	-1	53.221	23.8167	55.433	26.7707
		6	56.254	19.2981	65.367	12.2023
		Change	3.033	13.3186	9.933	24.4018
	Placebo	-1	63.388	22.8619	62.467	26.0972
		6	56.171	21.8066	57.738	23.0385
		Change	-7.217	15.7032	-4.729	22.8861
GIP AUC_{0-4h} (h·ng/L) §	Ipragliflozin	-1	530.246	164.6796	616.121	160.0223
		6	621.781	160.8757	672.869	178.5828
		Change	91.535	84.8803	56.748	129.9610
	Placebo	-1	551.654	117.1374	599.615	146.5592
		6	576.048	123.1420	615.126	175.6780
		Change	24.393	82.6858	15.511	110.1004
GIP C_{max} (ng/L) §	Ipragliflozin	-1	196.658	72.0317	245.833	58.4275
		6	240.758	63.2769	277.917	78.4513
		Change	44.100	41.3706	32.083	66.1185
	Placebo	-1	215.867	53.3187	239.775	62.4716
		6	217.608	55.0746	254.975	64.1961
		Change	1.742	39.8802	15.200	75.0064

All subjects in the Safety Analysis Set (SAF) who had at least one evaluable set of blood glucose or insulin data after dosing (Pharmacodynamic Analysis Set [PDAS]); n = 12 for each treatment group.

GIP: gastric inhibitory polypeptide; GLP-1: glucagon-like-peptide 1; Min: minimum; Max: maximum; OGTT: oral glucose tolerance test; PYY 3-36: Peptide YY 3-36 (intestinal hormone, saturation hormone); SD: standard deviation; T2DM: type 2 diabetic mellitus.

† Change from baseline (i.e., day 6 result minus day -1 result)

‡ Values below LLOQ [redacted] set to LLOQ/2 [redacted]

§ Values below LLOQ [redacted] set to LLOQ/2 [redacted]

Source: Tables 12.5.4.2, 12.5.4.8, 12.5.4.12, 12.5.4.16, 12.5.4.20 and 12.5.4.24

In the healthy subjects, no change in OGTT glucose AUCs after 6 days treatment with ipragliflozin 100 mg once daily was observed, compared to placebo (95% CIs for LS-mean difference ipragliflozin – placebo include zero). In the T2DM patients, however, glucose AUCs on day 6 were smaller (95% CIs for LS-mean difference ipragliflozin – placebo below zero), indicating a bigger glucose-lowering effect of ipragliflozin in patients with T2DM than in healthy subjects. Differences between healthy subjects and T2DM patients regarding the baseline-adjusted response (ipragliflozin – placebo) in OGTT insulin AUCs after 6 days treatment were also indicated. The results demonstrate that ipragliflozin exhibited a glucose-lowering effect in patients with T2DM while such an effect was not evident in healthy subjects.

In the healthy subjects, no change in OGTT glucagon AUCs was observed after 6 days treatment with ipragliflozin 100 mg once daily, compared to placebo. In the T2DM patients, glucagon AUCs were larger with ipragliflozin on day 6 (95% CIs for LS-mean difference ipragliflozin – placebo above zero), suggesting a less marked reduction of glucagon after the OGTT. However, differences between healthy subjects and T2DM

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patients regarding the baseline-adjusted response (ipragliflozin – placebo) in OGTT glucagon AUCs after 6 days treatment were statistically indicated only for the AUC_{0-2h}.

No changes at the OGTT could statistically be demonstrated for insulin, GLP-1, PYY 3-36 and GIP, neither for healthy subjects nor for patients with T2DM.

Urinary Glucose Excretion Results

Table 7 summarizes the results of the UGE_{0-24h} measurements on the different days for healthy subjects and patients with T2DM.

Table 7 Summary Statistics of UGE_{0-24h} (mmol) in Healthy Subjects and T2DM Patients on Different Days of Repeated Dosing With 100 mg Once Daily Ipragliflozin or Placebo (PDAS)

Treatment	Day/ Change †	Healthy Subjects			T2DM Patients		
		n	Mean	SD	n	Mean	SD
Ipragliflozin	Day -1	12	1.029	1.6063	10	70.775	87.0800
	Day 1	12	262.025	72.2990	12	618.759	184.0004
	Change	12	260.996	72.0943	10	520.769	96.9719
	Day 2	12	267.594	91.5376	12	711.152	184.1724
	Change	12	266.566	91.6268	10	599.831	101.4508
	Day 3	12	265.990	86.8240	12	675.510	182.7445
	Change	12	264.961	86.7017	10	575.105	98.0030
	Day 4	12	254.300	96.0261	12	665.755	214.9493
	Change	12	253.272	96.0518	10	540.503	118.0048
	Day 5	12	258.110	90.3337	12	637.667	151.8265
	Change	12	257.082	90.1737	10	536.952	93.9649
	Day 6	12	251.152	103.4660	12	518.118	129.9966
	Change	12	250.124	103.1367	10	433.971	97.7839
Placebo	Day -1	12	0.808	0.8758	11	98.096	181.7362
	Day 1	12	0.579	0.4835	12	117.119	207.5052
	Change	12	-0.230	0.8798	11	14.580	43.8921
	Day 2	12	0.478	0.2025	12	133.733	186.3634
	Change	12	-0.330	0.8676	11	30.224	56.0181
	Day 3	12	0.502	0.2418	11	142.767	193.8812
	Change	12	-0.306	0.8792	11	44.672	60.2231
	Day 4	12	0.478	0.1464	12	155.790	190.5340
	Change	12	-0.330	0.8412	11	45.112	79.9571
	Day 5	12	0.526	0.2261	12	144.695	183.4398
	Change	12	-0.283	0.7867	11	38.897	59.9087
	Day 6	12	1.854	3.8723	12	96.422	104.4480
	Change	12	1.046	3.0152	11	-2.168	93.4595

All subjects in the Safety Analysis Set (SAF) who had at least one evaluable set of blood glucose or insulin data after dosing (Pharmacodynamic Analysis Set [PDAS]).

UGE (mmol) calculated as urine volume (L) · glucose concentration in urine (mmol/L).

Urine volume (L) calculated as urine weight (kg) / specific gravity.

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Table 7 footnote continued

Glucose values below LLOQ have been set to LLOQ/2.

Min: minimum; Max: maximum; SD: standard deviation; T2DM: type 2 diabetes mellitus; UGE: urinary glucose excretion.

† Change from baseline (i.e., respective day minus day -1 result)

Source: Table 12.5.5.1.1

In both healthy subjects and patients with T2DM, an increase in UGE_{0-24h} on day 6 could be demonstrated for ipragliflozin 100 mg once daily in comparison to placebo (95% CIs for LS-mean difference ipragliflozin – placebo above zero), and the extent of excretion was higher in T2DM patients than in healthy subjects (95% CIs for LS-mean difference healthy – T2DM regarding the baseline-adjusted response (ipragliflozin – placebo) below zero).

24-Hour Urine Volume

Table 8 summarizes the results of the 24h-hour urine volume measurements on day -1 and day 6 for healthy subjects and patients with T2DM.

Table 8 Summary Statistics of 24-hourUrine Volume (L) in Healthy Subjects and T2DM Patients on Day -1 and on Day 6 of Repeated Dosing With 100 mg Once Daily Ipragliflozin or Placebo (PDAS)

Treatment	Day/ Change †	Healthy Subjects			T2DM Patients		
		n	Mean	SD	n	Mean	SD
Ipragliflozin	Day -1	12	2.599	0.7210	10	2.598	0.4715
	Day 6	12	2.869	0.6865	12	2.820	0.9305
	Change	12	0.270	0.4398	10	0.220	0.6868
Placebo	Day -1	12	2.847	0.7242	11	2.704	0.5591
	Day 6	12	2.767	1.0172	12	2.488	0.5682
	Change	12	-0.080	1.0902	11	-0.162	0.5325

All subjects in the Safety Analysis Set (SAF) who had at least one evaluable set of blood glucose or insulin data after dosing (Pharmacodynamic Analysis Set [PDAS]).

Urine volume (L) calculated as urine weight (kg) / specific gravity.

Min: minimum; Max: maximum; SD: standard deviation; T2DM : type 2 diabetes mellitus.

† Change from baseline (i.e., day 6 minus day -1 result)

Source: Table 12.5.6.1

In both healthy subjects and patients with T2DM, no change in the 24-hour urine volume on day 6 was detected with ipragliflozin 100 mg once daily in comparison to placebo (95% CIs for LS-mean difference ipragliflozin – placebo include zero).

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Urinary Excretion of Glucose, Sodium and Creatinine, Sodium and Creatinine in Serum, and Renal Function Parameters

Table 9 summarizes the urinary glucose excretion results for different time intervals on day -1 and day 6 as well as the 24-hour sodium and creatinine excretion, serum sodium and creatinine, and renal function parameters (CL_{Cr}, eGFR, cystatin C) on day 5 for healthy subjects and patients with T2DM.

Table 9 Summary Statistics of Urinary Glucose, Sodium and Creatinine Excretion, Serum Sodium and Creatinine, Creatinine Clearance, Estimated Glomerular Filtration Rate and Cystatin C in Healthy Subjects and T2DM Patients on Day 6 or Day 5 of Repeated Dosing of 100 mg Once Daily Ipragliflozin or Placebo (PDAS)

Parameter (Unit)	Treatment	Day/ Change †	Healthy Subjects		T2DM Patients	
			Mean	SD	Mean	SD
$Ae_{0\text{-}2h(Glu)}$ (mmol)	Ipragliflozin	-1	0.543	1.5294	18.037	12.0728
		6	43.573	14.0553	69.254	16.5536
		Change	43.030	13.3329	51.217	19.5281
	Placebo	-1	0.307	0.7100	16.624	11.9235
		6	0.523	1.3700	15.077	10.8993
		Change	0.216	0.6637	-1.546	6.0541
$Ae_{2\text{-}6h(Glu)}$ (mmol)	Ipragliflozin	-1	0.111	0.0764	29.307	20.6154
		6	44.195	17.2036	113.549	39.0879
		Change	44.084	17.1763	84.242	27.1166
	Placebo	-1	0.164	0.1797	31.707	30.2561
		6	0.411	0.8667	32.848	28.5282
		Change	0.247	0.6938	1.142	7.7996
$Ae_{0\text{-}6h(Glu)}$ (mmol)	Ipragliflozin	-1	0.654	1.5884	47.344	30.1094
		6	87.768	28.4023	182.803	45.2937
		Change	87.114	27.7968	135.459	34.2149
	Placebo	-1	0.471	0.8867	48.331	39.6726
		6	0.934	2.2348	47.926	37.4306
		Change	0.463	1.3547	-0.405	9.6909
$Ae_{0\text{-}24h(Na)}$ (mmol)	Ipragliflozin	5	192.502	29.1083	184.543	35.7975
	Placebo	5	186.830	25.0458	170.725	40.6460
$Ae_{0\text{-}24h(Cr)}$ (mmol)	Ipragliflozin	5	12.900	4.0103	11.415	3.1416
	Placebo	5	12.175	3.8234	11.320	3.1168
Serum Sodium (mmol/L)	Ipragliflozin	5	139.727	2.6867	139.917	0.9962
	Placebo	5	141.667	1.7753	139.000	1.7581
Serum Creatinine (mcmol/L)	Ipragliflozin	5	80.583	16.8341	78.533	16.0223
	Placebo	5	75.225	15.5684	75.067	13.2160
CL_{Cr} (L/h)	Ipragliflozin	5	6.596	1.2268	6.084	1.4006
	Placebo	5	6.714	1.5491	6.296	1.5837
eGFR (mL/min per 1.73 m²)	Ipragliflozin	5	84.858	12.0671	85.267	13.3634
	Placebo	5	91.600	11.0498	88.992	11.7478
Cystatin C (mg/L)	Ipragliflozin	5	0.780	0.0870	0.889	0.1371
	Placebo	5	0.778	0.0779	0.817	0.1136

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Table 9 footnote continued

All subjects in the Safety Analysis Set (SAF) who had at least one evaluable set of blood glucose or insulin data after dosing (Pharmacodynamic Analysis Set [PDAS]); n = 12 for each treatment group.
Min: minimum; Max: maximum; SD: standard deviation.
† Change from baseline (only for glucose excretion) defined as change from baseline (i.e., day 6 minus day -1 result)
Source: Tables 12.5.8.1, 12.5.9.1, 12.5.10.1, 12.5.11.1, 12.5.12.1, 12.5.13.1, 12.5.14.1 and 12.5.15.1

In both healthy subjects and patients with T2DM, an increase in $Ae_{0\text{-}2h(Glu)}$, $Ae_{2\text{-}6h(Glu)}$ and $Ae_{0\text{-}6h(Glu)}$ on day 6 could be demonstrated for ipragliflozin 100 mg once daily in comparison to placebo (95% CIs for LS-mean difference ipragliflozin – placebo above zero). $Ae_{2\text{-}6h(Glu)}$ and $Ae_{0\text{-}6h(Glu)}$ were larger for T2DM patients than for healthy subjects while a between-group difference in $A_{e0\text{-}2h(Glu)}$ could not be demonstrated with regard to the baseline-adjusted response (ipragliflozin – placebo).

No difference between ipragliflozin and placebo could be demonstrated for $Ae_{0\text{-}24h(Na)}$ on day 5.

In healthy subjects, $Ae_{0\text{-}24h(Cr)}$ on day 5 was higher with ipragliflozin 100 mg once daily, compared to placebo (95% CI for LS-mean difference ipragliflozin – placebo above zero), while in patients with T2DM no difference was detected. Between the 2 subject groups, no difference in $Ae_{0\ 24h(Cr)}$ could be demonstrated with regard to the difference ipragliflozin – placebo on day 5.

In healthy subjects, serum sodium concentrations on day 5 were lower with ipragliflozin 100 mg once daily than with placebo (95% CI for LS-mean difference ipragliflozin – placebo below zero) while in patients with T2DM no difference was detected. Between the 2 subject groups, a difference in serum sodium on day 5 was also indicated with regard to the difference ipragliflozin – placebo on day 5. Since mean and median sodium concentrations remained within the normal limits, the finding is considered of little relevance.

In both healthy subjects and patients with T2DM, serum creatinine concentrations on day 5 were higher with ipragliflozin 100 mg once daily than with placebo (95% CIs for LS-mean difference ipragliflozin – placebo above zero) while there was no difference indicated between the 2 subject groups with regard to the difference ipragliflozin – placebo on day 5. Since mean and median creatinine concentrations remained within the normal limits, the finding is considered of little relevance.

The descriptive evaluation of renal function parameters suggests that 100 mg ipragliflozin, in healthy subjects as well as in patients with T2DM, did not exhibit major influence on renal function, as represented by renal clearance, eGFR, and cystatin C in serum.

Energy Production and Substrate Utilization

Table 10 summarizes the results for the various parameters of energy production and substrate utilization, as measured by means of indirect calorimetry on day -7 and on day 4.

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Table 10 Summary Statistics of Energy Production and Substrate Utilization Parameters in Healthy Subjects and T2DM Patients at Baseline and on Day 4 of Repeated Dosing of 100 mg Once Daily Ipragliflozin or Placebo (PDAS)

Parameter (Unit)	Treatment	Day/ Change †	Healthy Subjects		T2DM Patients	
			Mean	SD	Mean	SD
RMR (kcal/day)	None	-7	1601.250	281.4108	1715.417	247.1093
	Ipragliflozin	4	1555.583	422.2168	1630.750	251.8940
		Change	-45.667	185.5245	-84.667	145.7615
	Placebo	4	1582.000	311.3087	1679.333	256.7876
		Change	-19.250	180.1248	-36.083	127.0200
V_{O2} (mL/min)	None	-7	232.167	39.9996	251.750	36.4146
	Ipragliflozin	4	224.083	59.9825	239.000	37.5621
		Change	-8.083	27.6256	-12.750	21.4778
	Placebo	4	229.083	45.9079	244.000	36.9939
		Change	-3.083	26.7903	-7.750	17.8638
V_{CO2} (mL/min)	None	-7	188.083	37.6647	192.000	28.5593
	Ipragliflozin	4	187.083	54.9437	184.167	28.0967
		Change	-1.000	21.9379	-7.833	19.1066
	Placebo	4	186.833	35.2906	195.500	31.6213
		Change	-1.250	22.2593	3.500	19.6260
RER	None	-7	0.804	0.0635	0.758	0.0416
	Ipragliflozin	4	0.823	0.0509	0.768	0.0447
		Change	0.019	0.0474	0.010	0.0441
	Placebo	4	0.811	0.0432	0.797	0.0370
		Change	0.007	0.0548	0.039	0.0472
CHO (g/min)	None	-7	0.096	0.0613	0.057	0.0378
	Ipragliflozin	4	0.114	0.0656	0.062	0.0431
		Change	0.018	0.0421	0.005	0.0432
	Placebo	4	0.101	0.0381	0.094	0.0407
		Change	0.004	0.0518	0.037	0.0482
FAT (g/min)	None	-7	0.075	0.0243	0.101	0.0229
	Ipragliflozin	4	0.064	0.0232	0.093	0.0265
		Change	-0.011	0.0226	-0.009	0.0208
	Placebo	4	0.072	0.0257	0.082	0.0197
		Change	-0.003	0.0261	-0.019	0.0192

All subjects in the Safety Analysis Set (SAF) who had at least one evaluable set of blood glucose or insulin data after dosing (Pharmacodynamic Analysis Set [PDAS]); n = 12 for each treatment group.

CHO: carbohydrate oxidation rate; FAT: lipid oxidation rate; Min: minimum; Max: maximum;
RER: respiratory exchange ratio; RMR: resting metabolic rate; SD: standard deviation; T2DM: type 2 diabetes mellitus; VCO2: carbon dioxide production; VO2: oxygen consumption.

† Change from baseline (i.e., day 4 minus day -7 result). Day -7 was baseline for both treatment periods.

Source: Table 12.5.7.1

Both in healthy and T2DM patients, no change from baseline could statistically be demonstrated for any of the above parameters.

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Pharmacodynamic Results Part B:

24-Hour Urinary Glucose Excretion

Table 11 summarizes the results of the UGE_{0-24h} measurements on the different days in T2DM patients treated with 12.5 and 100 mg ipragliflozin.

Table 11 Summary Statistics of Urinary Glucose Excretion in T2DM Patients on Different Days of Repeated Dosing With 12.5 or 100 mg Once Daily Ipragliflozin (PDAS)

Day/ Change †	Ipragliflozin 12.5 mg			Ipragliflozin 100 mg		
	n	Mean	SD	n	Mean	SD
Day -1	19	25.344	34.6627	20	40.335	50.0674
Day 1	20	245.862	123.9182	19	514.217	226.7345
Change	19	206.808	94.6341	19	473.035	192.4505
Day 2	20	266.050	123.2882	20	572.650	226.3732
Change	19	229.193	94.3377	20	532.316	193.1155
Day 3	20	283.810	138.5913	20	577.219	232.9780
Change	19	249.127	113.8627	20	536.884	199.4494
Day 4	20	268.200	132.6189	20	580.955	246.1725
Change	19	232.787	108.8201	20	540.620	220.7079
Day 5	19	250.021	124.2887	20	526.802	220.6452
Change	18	213.689	98.4742	20	486.468	193.6146

All subjects in the Safety Analysis Set (SAF) who had at least one evaluable set of blood glucose or insulin data after dosing (Pharmacodynamic Analysis Set [PDAS]).

Min: minimum; Max: maximum; SD standard deviation ; T2DM : type 2 diabetes mellitus.

† Change from baseline (i.e., respective day minus day -1 result)

UGE (mmol) calculated as urine volume (L) · glucose concentration in urine (mmol/L)

Urine volume (L) calculated as urine weight (kg) / specific gravity

Source: Table 12.5.1.1

Descriptive evaluation of the results demonstrates that, in patients with T2DM, mean urinary glucose excretion over 24 hours was increased already after the first dose administration and remained at this level for at least 5 days when dosing was continued. There was a dose-dependency of the amount of excreted glucose.

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Plasma Glucose

Table 12 summarizes the results of $C_{average}$ and AUC_{0-24} of plasma glucose, as determined on day -1 and day 5.

Table 12 Summary Statistics of Plasma Glucose Parameters in T2DM Patients on Day -1 and Day 5 of Repeated Dosing With 12.5 or 100 mg Once Daily Ipragliflozin (PDAS)

Parameter (Unit)	Day/ Change †	Ipragliflozin 12.5 mg			Ipragliflozin 100 mg		
		n	Mean	SD	n	Mean	SD
$C_{average}$ of plasma glucose (mmol/L)	Day -1	20	9.729	1.8452	20	9.928	2.1143
	Day 5	20	9.097	1.6528	20	8.176	1.2255
	Change	20	-0.632	0.9995	20	-1.751	1.2417
Plasma Glucose AUC_{0-24h} (mmol·h/L)	Day -1	20	233.486	44.2843	20	238.268	50.7434
	Day 5	20	218.320	39.6675	20	196.232	29.4117
	Change	20	-15.166	23.9869	20	-42.036	29.8012

All subjects in the Safety Analysis Set (SAF) who had at least one evaluable set of blood glucose or insulin data after dosing (Pharmacodynamic Analysis Set [PDAS]).

Min: minimum; Max: maximum; SD: standard deviation: T2DM: type 2 diabetes mellitus.

† Change from baseline (i.e., day 5 minus day -1 result)

Source: Tables 12.5.2.1 and 12.5.2.2

Descriptive evaluation of the results demonstrates that, after treating patients with T2DM for 5 days, ipragliflozin exhibited a glucose-lowering effect (based on $C_{average}$ and AUC_{0-24h}) at a dose of 12.5 mg, which was more pronounced at a dose of 100 mg once daily.

Safety Results Part A:

Overall, 56 treatment-emergent adverse events (TEAEs) were reported in Part A of this study. Forty-eight AEs were reported in the healthy subjects group (22 with ipragliflozin 100 mg, 26 with placebo) and 8 in the T2DM patients group (3 with ipragliflozin 100 mg, 5 with placebo). There were no deaths, serious adverse events (SAEs) or AEs leading to discontinuation.

Overall, 33 AEs were assessed as drug-related, 29 in the healthy subjects group (13 with ipragliflozin 100 mg, 16 with placebo) and 4 in the T2DM patients group (1 with ipragliflozin 100 mg, 3 with placebo). For all those events, the relationship to study drug was rated as “possible”. The events were diarrhea, dyspepsia, flatulence, hypoglycemia, hypoglycemia unawareness, back pain, myalgia, headache, rash and hot flush.

The majority of AEs was assessed as being “mild”. Only 4 AEs (all in T2DM patients treated with placebo) were assessed as being “moderate”. These events were back pain and myalgia in 1 subject, back pain in a second subject, and dyspepsia in a third subject. None of the AEs had the rating “severe”.

The majority of AEs occurred in the healthy subjects group. Within the 2 groups, events were fairly equally distributed among treatments. In particular, hypoglycemic events occurred solely in healthy subjects. However, except for one case of hypoglycemia under ipragliflozin, these were instances of hypoglycemia unawareness, equally distributed among ipragliflozin and placebo treatment. The case of symptomatic

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hypoglycemia (mild) occurred 6 hours after dosing with 100 mg ipragliflozin on day 6 (i.e., 4 hours after OGTT glucose ingestion) and lasted for 2.43 hours. No treatment was required for this event.

Table 13 Summary of Treatment-emergent Adverse Events Part A (SAF)

System Organ Class / Preferred Term	Healthy Subjects				T2DM Patients			
	Ipragliflozin 100 mg (n = 12)		Placebo (n = 12)		Ipragliflozin 100 mg (n = 12)		Placebo (n = 12)	
Overall	**11 (91.7%)**	**22**	**12 (100%)**	**26**	**3 (25.0%)**	**3**	**4 (33.3%)**	**5**
Gastrointestinal disorders	**0**	**0**	**3 (25.0%)**	**3**	**0**	**0**	**1 (8.3%)**	**1**
Abdominal pain upper	0	0	1 (8.3%)	1	0	0	0	0
Diarrhoea	0	0	1 (8.3%)	1	0	0	0	0
Dyspepsia	0	0	0	0	0	0	1 (8.3%)	1
Flatulence	0	0	1 (8.3%)	1	0	0	0	0
Infections and infestations	**0**	**0**	**0**	**0**	**1 (8.3%)**	**1**	**0**	**0**
Nasopharyngitis	0	0	0	0	1 (8.3%)	1	0	0
Injury, poisoning and procedural complications	**1 (8.3%)**	**1**	**0**	**0**	**0**	**0**	**0**	**0**
Contusion	1 (8.3%)	1	0	0	0	0	0	0
Metabolism and nutrition disorders	**9 (75.0%)**	**16**	**11 (91.7%)**	**17**	**0**	**0**	**0**	**0**
Hypoglycaemia	1 (8.3%)	1	0	0	0	0	0	0
Hypoglycaemia unawareness	9 (75.0%)	15	11 (91.7%)	17	0	0	0	0
Musculoskeletal and connective tissue disorders	**1 (8.3%)**	**1**	**2 (16.7%)**	**2**	**1 (8.3%)**	**1**	**2 (16.7%)**	**3**
Back pain	1 (8.3%)	1	1 (8.3%)	1	1 (8.3%)	1	2 (16.7%)	2
Myalgia	0	0	1 (8.3%)	1	0	0	1 (8.3%)	1
Nervous system disorders	**3 (25.0%)**	**3**	**3 (25.0%)**	**3**	**0**	**0**	**1 (8.3%)**	**1**
Headache	3 (25.0%)	3	3 (25.0%)	3	0	0	1 (8.3%)	1
Skin and subcutaneous tissue disorders	**0**	**0**	**0**	**0**	**1 (8.3%)**	**1**	**0**	**0**
Rash	0	0	0	0	1 (8.3%)	1	0	0
Vascular disorders	**1 (8.3%)**	**1**	**1 (8.3%)**	**1**	**0**	**0**	**0**	**0**
Hot flush	0	0	1 (8.3%)	1	0	0	0	0
Orthostatic hypotension	1 (8.3%)	1	0	0	0	0	0	0

All subjects who were randomized to receive study treatment and who received at least 1 dose of study medication (Safety Analysis Set [SAF]). Within a system organ class, patients may have reported more than one type of AE. Treatment-emergent adverse events (TEAEs) were AEs that occurred after the first dose of study drug during the relevant treatment period.

First column: number of subjects experiencing AEs followed by percentage of subjects based on number of subjects exposed per treatment (in parentheses); second column: number of events.

T2DM: type 2 diabetes mellitus.

Source: Table 12.6.1.2.1

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There were no clinically relevant changes in safety laboratory test results (hematology, biochemistry, urinalysis), ECG recordings, or physical examination findings. There were no clinically relevant changes from baseline in systolic and diastolic blood pressure, pulse rate and weight.

Safety Results Part B:

Overall, 13 TEAEs were reported in Part B of this study. Four AEs were reported at the 12.5 mg and 9 at the 100 mg ipragliflozin dose. There were no deaths, other serious adverse events (SAEs) or AEs leading to discontinuation.

Overall, 6 AEs were assessed as drug-related, 3 with 12.5 mg and 3 with 100 mg ipragliflozin. For all those events, the relationship to study drug was rated as "possible". The events were diarrhea, flatulence, hypoglycemia and muscle spasms. AEs other than gastrointestinal disorders occurred solely at the 100 mg ipragliflozin dose.

The majority of AEs was assessed as being "mild". Only 1 AE (urinary tract infection, 100 mg ipragliflozin) was assessed as being "moderate". None of the AEs had the rating "severe".

One case of symptomatic hypoglycemia (mild) occurred approximately 7 hours after dosing with 100 mg ipragliflozin on day 4 and lasted for 0.56 hours. The event was treated with oral glucose administration.

The total number of AEs experienced at the 100 mg ipragliflozin dose was more than twice that at the 12.5 mg dose (9 vs 4). However, taking into account the drug-relationship assessment where 3 AEs under each treatment were assessed as drug-related, no correlation between ipragliflozin dose level and occurrence of adverse events was evident.

Table 14 Summary of Treatment-emergent Adverse Events Part B (SAF)

System Organ Class / Preferred Term	**Ipragliflozin 12.5 mg (n = 20)**		**Ipragliflozin 100 mg (n = 20)**	
Overall	**3 (15.0%)**	**4**	**6 (30.0%)**	**9**
Gastrointestinal disorders	**3 (15.0%)**	**4**	**2 (10.0%)**	**2**
Diarrhoea	1 (5.0%)	2	1 (5.0%)	1
Flatulence	1 (5.0%)	1	1 (5.0%)	1
Vomiting	1 (5.0%)	1	0	0
Infections and infestations	**0**	**0**	**2 (10.0%)**	**2**
Nasopharyngitis	0	0	1 (5.0%)	1
Urinary tract infection	0	0	1 (5.0%)	1
Metabolism and nutrition disorders	**0**	**0**	**1 (5.0%)**	**1**
Hypoglycaemia	0	0	1 (5.0%)	1
Table continued on next page				

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Table 14 continued

System Organ Class / Preferred Term	Ipragliflozin 12.5 mg (n = 20)		Ipragliflozin 100 mg (n = 20)	
Musculoskeletal and connective tissue disorders	**0**	**0**	**1 (5.0%)**	**1**
Muscle spasms	0	0	1 (5.0%)	1
Nervous system disorders	**0**	**0**	**1 (5.0%)**	**2**
Headache	0	0	1 (5.0%)	2
Renal and urinary disorders	**0**	**0**	**1 (5.0%)**	**1**
Oliguria	0	0	1 (5.0%)	1

All subjects who were randomized to receive study treatment and who received at least 1 dose of study medication (Safety Analysis Set [SAF]). Within a system organ class, patients may have reported more than one type of AE. Treatment-emergent adverse events (TEAEs) were AEs that occurred after the first dose of study drug during the relevant treatment period.

First column: number of subjects experiencing AEs followed by percentage of subjects based on number of subjects exposed per treatment (in parentheses); second column: number of events.

Source: Table 12.6.1.2.1

There were no clinically relevant changes in safety laboratory test results (hematology, biochemistry, urinalysis), ECG recordings, or physical examination findings. There were no clinically relevant changes from baseline in systolic and diastolic blood pressure, pulse rate and weight.

CONCLUSIONS:

Pharmacokinetic Conclusions Part A:

- Systemic exposure to ipragliflozin, 100 mg administered orally once daily for 6 days, was similar in healthy subjects and patients with T2DM (mean AUC_{tau} on day 6: 8067 and 8152 ng·h/mL; mean C_{max}: 1502 and 1711 ng/mL, respectively).
- In both subject groups, steady state conditions were reached after 4 days of dosing with ipragliflozin, with a mean PTR on day 6 of 18 (healthy subjects) and 20 (T2DM patients).
- Mean apparent total body clearance (CL/F) on day 6 was 13 L/h in both subject groups.
- Following oral administration of ipragliflozin 100 mg once daily for 6 days, systemic exposure to the metabolite M2 was higher in patients with T2DM than in healthy subjects (mean AUC_{tau} on day 6: 7117 and 5427 ng·h/mL; mean C_{max}: 1228 and 959 ng/mL, respectively).

Pharmacokinetic Conclusions Part B:

- Systemic exposure to 12.5 and 100 mg ipragliflozin, administered orally once daily for 5 days, was dose-proportional according to descriptive data (mean AUC_{tau} on day 5: 883 and 6904 ng·h/mL; mean C_{max}: 192 and 1263 ng/mL, respectively).
- At both dose levels, steady state conditions were reached after 4 days of dosing with ipragliflozin, with a mean PTR on day 5 of 19 (12.5 mg) and 16 (100 mg).

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- Both t_{max} and CL/F were consistent across the tested doses (mean t_{max} on day 5: 2.0 and 2.1 hours for 12.5 and 100 mg, respectively; mean CL/F: 15 L/h for both doses).
- Following oral administration of 12.5 and 100 mg ipragliflozin once daily for 5 days, systemic exposure to the metabolite M2 was dose-proportional (mean AUC_{tau} on day 5: 653 and 5087 ng·h/mL; mean C_{max}: 127 and 790 ng/mL, respectively).

Pharmacodynamic Conclusions Part A:

- Ipragliflozin, 100 mg administered orally once daily for 6 days, increased EGP_{basal} as well as $R_{d\ basal}$ both in healthy subjects and patients with T2DM, as shown in comparison to placebo.
- Ipragliflozin treatment resulted in a less pronounced suppression of EGP at the OGTT in both subject groups.
- A trend to an increased R_d at the OGTT was observed with ipragliflozin, in particular in T2DM patients. However, this finding could not be supported statistically.
- Mean $R_{d\ basal}$ corrected for UGE decreased, compared to placebo, with ipragliflozin in both subject groups but the decrease was larger and statistically indicated in the T2DM group only.
- Both in healthy subjects and T2DM patients, mean $R_{d\ OGTT}$ corrected for UGE in the time interval 0 to 6 h decreased, compared to placebo, with ipragliflozin.
- No change under ipragliflozin treatment, compared to placebo, could be demonstrated for ΔEGP, $R_{a\ OGTT,}$ $R_{a\ (total),}$ and $R_{d\ OGTT}$ in the 6-hour interval after OGTT, neither for healthy subjects nor for patients with T2DM.
- Glucose bioavailability was approximately 100% at all OGTTs.
- Ipragliflozin, 100 mg administered orally once daily for 6 days, exhibited a glucose-lowering effect in patients with T2DM, as shown by an OGTT on day 6 of treatment in comparison to placebo. In healthy subjects, such an effect could not be demonstrated.
- No effects of ipragliflozin at the OGTT were observed for plasma insulin, GLP-1, PYY 3-36 and GIP.
- There was a less pronounced reduction of plasma glucagon concentrations at the OGTT in T2DM patients treated with ipragliflozin while such an effect was not evident in healthy subjects. However, a difference between the 2 subject groups could not be demonstrated.
- Ipragliflozin, 100 mg administered orally once daily for 6 days, resulted in an increase in urinary glucose excretion, as shown by $UGE_{0\text{-}24h}$ on day 6 of treatment, in both healthy and T2DM patients and in comparison to placebo.
- Ipragliflozin had no impact on the excreted urine volume, neither of healthy subjects nor of T2DM patients.

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- No effect of ipragliflozin on urinary sodium excretion was observed, as shown by the amount of sodium excreted over 24 hours on day 5.
- A higher urinary creatinine excretion on day 5 was observed, compared to placebo, with ipragliflozin in healthy subjects while in patients with T2DM such a difference was not evident. However, a difference between the 2 subject groups could not be demonstrated.
- Lower serum sodium concentrations on day 5 were observed, compared to placebo, with ipragliflozin in healthy subjects while in patients with T2DM such a difference was not evident.
- Higher serum creatinine concentrations on day 5 were observed, compared to placebo, with ipragliflozin in healthy subjects as well as in patients with T2DM.
- Ipragliflozin administration had no major impact on renal function (as represented by CL_{Cr}, eGFR and serum cystatin C concentrations determined on day 5), neither in healthy subjects nor in patients with T2DM.
- On the investigated parameters of energy production and substrate utilization (RMR, V_{O2}, $VC_{O2,}$ FAT, RER and CHO), ipragliflozin had no statistically demonstrated impact, neither in healthy subjects nor in T2DM patients.

Pharmacodynamic Conclusions Part B:

- Ipragliflozin, administered orally at doses of 12.5 and 100 mg once daily to patients with T2DM for 5 consecutive days, increased mean 24-hour urinary glucose excretion. The effect was evident already after the first dose and remained at this level for the 5 treatment days.
- The amount of excreted glucose was dose-dependent.
- Ipragliflozin exhibited a glucose-lowering effect (based on mean $C_{average}$ and mean AUC_{0-24h} on day 5) at the 12.5 mg and at the 100 mg dose.

Safety Conclusions Part A:

- Eleven (91.7%) healthy subjects experienced 22 TEAEs with ipragliflozin 100 mg and 12 (100%) experienced 26 TEAEs with placebo.
- Three (25.0%) T2DM patients experienced 3 TEAEs with ipragliflozin 100 mg and 4 (33.3%) experienced 5 TEAEs with placebo.
- In the healthy subjects group, the most commonly experienced TEAEs by SOC were “metabolism and nutrition disorders” (16 with ipragliflozin and 17 with placebo) while “musculoskeletal and connective tissue disorders” were most common in the T2DM patients group (1 with ipragliflozin and 3 with placebo).
- Apart from “gastrointestinal disorders”, which were reported 3 times with placebo but not with ipragliflozin, all TEAEs were fairly evenly distributed across the treatments.

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- The number of drug-related TEAEs was higher in the healthy (29) than in the T2DM patients group (4) but across treatments, drug-related TEAEs were similarly distributed.
- The majority of TEAEs were of mild severity; 4 TEAEs were of moderate severity and were experienced by T2DM patients with placebo treatment. There were no severe TEAEs.
- No deaths or serious adverse events were reported during this study part.
- There were no adverse events that resulted in permanent discontinuation from the study.
- No clinically relevant changes in the laboratory tests for hematology, biochemistry and urinalysis were observed.
- There were no clinically relevant changes from baseline in systolic and diastolic blood pressure, pulse rate and weight.
- There were no clinically relevant changes in ECG and physical examination findings.
- Overall, oral administration of 100 mg ipragliflozin once daily for consecutive 6 days was well tolerated and did not raise any safety concerns.

Safety Conclusions Part B:

- Three (15.0%) T2DM patients experienced 4 TEAEs with 12.5 mg ipragliflozin and 6 (30%) experienced 9 TEAEs with 100 mg ipragliflozin.
- The most commonly experienced TEAEs by SOC were “gastrointestinal disorders” (4 with 12.5 and 2 with 100 mg ipragliflozin).
- While with 12.5 mg ipragliflozin TEAEs comprised only “gastrointestinal disorders, TEAEs at the 100 mg dose included several more organ systems but only in single subjects.
- The number of drug-related TEAEs was equal (3) at both doses.
- The majority of TEAEs were of mild severity; 1 TEAE of moderate severity was experienced with 100 mg ipragliflozin. There were no severe TEAEs.
- No deaths or serious adverse events were reported during this study part.
- There were no adverse events that resulted in permanent discontinuation from the study.
- No clinically relevant changes in the laboratory tests for hematology, biochemistry and urinalysis were observed.
- There were no clinically relevant changes from baseline in systolic and diastolic blood pressure, pulse rate and weight.
- There were no clinically relevant changes in ECG and physical examination findings.

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- Overall, oral administration of 12.5 and 100 mg ipragliflozin, each dose given once daily for 5 consecutive days, was well tolerated and did not raise any safety concerns.

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