Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Ipragliflozin		
Name of Active Ingredient: Ipragliflozin (ASP1941)		

SYNOPSIS

Title of Study: Phase 2b, Double-Blind, Randomized, Multicenter, Parallel Group, Placebo-Controlled, Dose-Finding Study to Evaluate the Efficacy, Safety and Tolerability of a 12-Week Treatment with ASP1941 in Combination with Metformin in Patients with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin Alone

Investigators/Coordinating Investigator: [redacted] DM FRCP, [redacted], UK

Study Center(s): This study was conducted in 46 active study centers in 6 countries (UK, Italy; Hungary, Poland, Romania; and US).

Publication (reference): None

Study Period: Approximately 18 weeks.

Date of first enrollment (Study initiation date): 06 Apr 2010

Date of last evaluation (Study completion date): 01 Apr 2011

Phase of Development: Phase 2b

Objectives: The primary objective of the study was to evaluate the efficacy of a 12-week treatment of 4 doses of ipragliflozin in combination with metformin compared to placebo in combination with metformin in patients with type 2 diabetes mellitus (T2DM) who had inadequate glycemic control on metformin alone. Secondary objectives were to evaluate the safety and tolerability, pharmacodynamics and pharmacokinetics of 4 doses of ipragliflozin in combination with metformin compared to placebo in combination with metformin.

Methodology: This was a 12-week, phase 2b, multicenter, double-blind, randomized, parallel-group, placebo controlled, dose-finding study in patients with T2DM who had inadequate glycemic control on metformin alone. The study consisted of a single-blind, 2-week placebo run-in period, followed by a randomized, double-blind, placebo-controlled, 12-week treatment period and a 4-week follow-up period.

Patients entering the study were receiving stable doses of metformin monotherapy at a dose of at least 1500 mg/day which had remained unaltered for the previous 6 weeks. The dose was kept stable throughout the study and patients continued to receive their usual brand of prescribed metformin.

A medical monitor assessed the overall safety throughout the study in a blinded fashion. A cardiovascular endpoint committee (CVEC) adjudicated all cardiovascular events as defined in the CVEC charter.

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Number of Patients (planned, enrolled and analyzed): It was planned that 63 patients would be randomized to each treatment group (315 patients in total). Assuming a run-in failure rate of 50%, it was expected that approximately 630 patients would be enrolled in the single-blind placebo run-in period. In total, 650 patients were screened, 343 patients were randomized to treatment and 306 (89.2%) completed the 12-week study.

Diagnosis and Main Criteria for Inclusion: Male or female patients with T2DM (for at least 6 months) and inadequate glycemic control (glycated hemoglobin [HbA_{1c}) levels between 7% and 9.5%) on stable metformin (≥ 1500 mg/day) monotherapy (for at least 6 weeks) were suitable candidates for study enrollment.

Test Product, Dose and Mode of Administration, Batch Numbers: Study treatments, ipragliflozin and ipragliflozin placebo to match (PTM), were supplied as 12.5 and 50 mg tablets. The daily oral dose of study drug was to be administered as an add-on to the daily oral dose of metformin (≥1500 mg/day). The dose administered was determined following randomization to one of the following 5 treatment groups:

Group 1: Ipragliflozin 12.5 mg once daily
Group 2: Ipragliflozin 50 mg once daily
Group 3: Ipragliflozin 150 mg once daily
Group 4: Ipragliflozin 300 mg once daily
Group 5: Ipragliflozin PTM once daily

Throughout the run-in and double-blind treatment period, patients took 7 tablets per day (Table 1).

Table 1 Number of Ipragliflozin Tablets Per Dose Group

	Ipragliflozin			
	12.5 mg	**PTM (12.5 mg)**	**50 mg**	**PTM (50 mg)**
Group 1: Ipragliflozin 12.5 mg	1	None	None	6
Group 2: Ipragliflozin 50 mg	None	1	1	5
Group 3: Ipragliflozin 150 mg	None	1	3	3
Group 4: Ipragliflozin 300 mg	None	1	6	None
Group 5: Placebo	None	1	None	6
PTM: placebo-to-match				

Ipragliflozin batch numbers were as follows:

- Ipragliflozin 12.5 mg: [redacted]
- Ipragliflozin 50 mg: [redacted], [redacted], [redacted], [redacted]

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Duration of Treatment (or Duration of Study, if applicable): The study consisted of a single-blind, 2-week placebo run-in period, followed by a randomized, double-blind, placebo-controlled, 12-week treatment period and a 4-week follow-up period.

Reference Product, Dose and Mode of Administration, Batch Numbers: PTM ipragliflozin tablets were provided.

Placebo batch numbers were as follows:

- Ipragliflozin 12.5 mg PTM: [redacted]
- Ipragliflozin 50 mg PTM: [redacted], [redacted], [redacted], [redacted], [redacted]

Criteria for Evaluation: The primary efficacy analysis was the change from baseline to week 12 in $HbA_{1c.}$

Secondary efficacy analyses included the following:

- Change from baseline in fasting plasma glucose (FPG) at Week 12 compared with placebo
- Achievement of target goal (HbA_{1c} < 7.0%) at Week 12 compared with placebo
- Achievement of target goal (HbA_{1c} < 6.5%) at Week 12 compared with placebo

Exploratory efficacy analyses included the following:

- [redacted]
- [redacted]
- [redacted]

Health outcomes were measured by the European Quality of Life–5 dimensions (EQ-5D), Audit of Diabetes-Dependent Quality of Life-19 (ADDQoL) and Diabetes Medication Satisfaction (Diab-MedSat) questionnaires.

Plasma levels of ipragliflozin and metformin were taken for population pharmacokinetic analysis. The pharmacokinetic/pharmacodynamic results are reported in a separate document [1941-PK-0003].

Safety was assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs)

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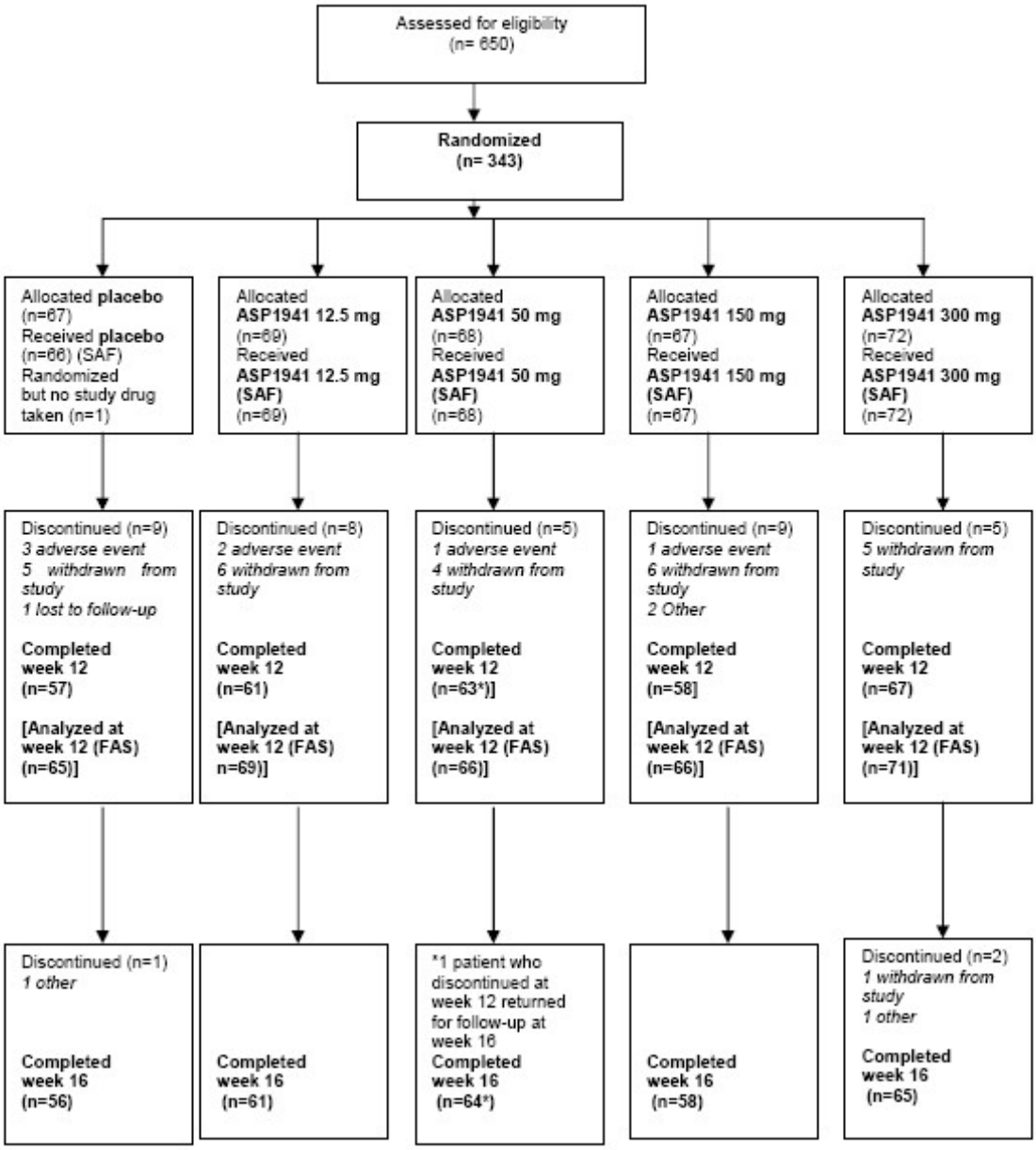
- Physical examinations
- Clinical laboratory assessments
- Hepatic parameters
- Vital signs
- 12-lead electrocardiogram (ECG) measurements

Statistical Methods: Descriptive statistics (n, mean, SD, minimum, median and maximum) for each visit were calculated for all variables. To compare changes in primary and most secondary efficacy variables, analysis of covariance (ANCOVA) was used with baseline values as the covariate, treatment group as fixed effects and site as a random effect. Last observation carried forward (LOCF) was used in the primary analysis and actual data were used in a secondary analysis. Pairwise comparisons with placebo were performed starting at the highest dose of ipragliflozin. If the P-value exceeded 0.05, doses at that level and lower were considered statistically insignificant. This sequential trend test was used to control for multiple comparisons. The Cochran-Armitage test for trend was applied to the proportion of patients who achieved a target goal of HbA_{1c} (of either < 6.5% or < 7.0%) in each of the ipragliflozin dose groups compared with placebo. The full analysis set (FAS) was used for the primary analysis. The per-protocol set (PPS) provided a supportive analysis of the FAS. The safety analysis set (SAF) consisted of all patients who received at least one dose of study medication. Safety data were summarized by descriptive statistics.

Summary of Results/Conclusions:

Population

Figure 1 Patient Disposition



Source: End of Text Tables 12.1.1.1, 12.1.1.2, 12.1.2.1, 12.1.2.2

Proportions of patients within each demographic characteristic were comparable between treatment groups and there was no statistically significant difference between treatment groups in terms of gender, ethnicity/race, age, total daily metformin dose, formulation of metformin used or time since diagnosis of T2DM (Table 2). Most patients were white, ≤65 years of age, had been diagnosed with T2DM within the previous 10 years, and received ≥ 2000 to < 3000 mg/day metformin which was administered twice daily and was not a modified release formulation.

Table 2 Demographic Characteristics - SAF

Parameter	Placebo	Ipragliflozin			
		12.5 mg qd	50 mg qd	150 mg qd	300 mg qd
	n=66	n=69	n=68	n=67	n=72
Gender					
Male	36 (54.5%)	33 (47.8%)	32 (47.1%)	38 (56.7%)	36 (50.0%)
Female	30 (45.5%)	36 (52.2%)	36 (52.9%)	29 (43.3%)	36 (50.0%)
P-value †	0.748				
Race					
White	63 (95.5%)	63 (91.3%)	66 (97.1%)	65 (97.0%)	65 (90.3%)
Non-white	3 (4.5%)	6 (8.7%)	2 (2.9%)	2 (3.0%)	7 (9.7%)
P-value†	0.265				
Race					
White	63 (95.5%)	63 (91.3%)	66 (97.1%)	65 (97.0%)	65 (90.3%)
Black or African American	3 (4.5%)	4 (5.8%)	1 (1.5%)	1 (1.5%)	7 (9.7%)
Asian	0	1 (1.4%)	0	1 (1.5%)	0
Other	0	1 (1.4%)	1 (1.5%)	0	0
P-value†	0.342				
Age group (years)					
< 65	52 (78.8%)	57 (82.6%)	55 (80.9%)	52 (77.6%)	58 (80.6%)
≥ 65	14 (21.2%)	12 (17.4%)	13 (19.1%)	15 (22.4%)	14 (19.4%)
P-value†	0.959				
Age (years)					
n	66	69	68	67	72
Mean	57.3	56.6	58.6	58.1	56.6
SD	8.55	8.53	7.60	8.24	8.93
Min	33	38	36	40	21
Median	57.5	55.0	58.0	58.0	57.0
Max	75	79	73	79	70
P-value§	0.515				
Total daily metformin dose					
≥ 1500 mg to < 2000 mg	21 (31.8%)	15 (21.7%)	24 (35.3%)	23 (34.3%)	26 (36.1%)
≥ 2000 mg to < 3000 mg	39 (59.1%)	48 (69.6%)	40 (58.8%)	42 (62.7%)	39 (54.2%)
≥ 3000 mg	6 (9.1%)	6 (8.7%)	4 (5.9%)	2 (3.0%)	7 (9.7%)
P-value†	0.488				

Table 2 continued on next page

Table 2 continued

Parameter	Placebo	Ipragliflozin			
		12.5 mg qd	50 mg qd	150 mg qd	300 mg qd
	n=66	n=69	n=68	n=67	n=72
Metformin as modified release					
Yes	3 (4.5%)	2 (2.9%)	0	2 (3.0%)	2 (2.8%)
No	63 (95.5%)	67 (97.1%)	68 (100.0%)	65 (97.0%)	70 (97.2%)
P-value†	0.585				
Metformin formulation					
qd	2 (3.0%)	1 (1.4%)	0	0	1 (1.4%)
bid	37 (56.1%)	36 (52.2%)	35 (51.5%)	46 (68.7%)	46 (63.9%)
tid	27 (40.9%)	32 (46.4%)	33 (48.5%)	20 (29.9%)	25 (34.7%)
qid	0	0	0	1 (1.5%)	0
P-value†	0.268				
T2DM diagnosis since (years)					
n	66	69	68	67	72
Mean	5.66	6.82	6.03	5.74	5.48
SD	3.22	6.37	5.25	4.80	4.82
Min	0.6	0.5	0.6	0.5	0.6
Median	5.72	4.89	4.13	4.65	4.43
Max	12.7	37.7	30.8	21.8	30.9
P-value§	0.547				
T2DM diagnosis since (years)					
< 10	61 (92.4%)	58 (84.1%)	58 (85.3%)	58 (86.6%)	61 (84.7%)
≥ 10	5 (7.6%)	11 (15.9%)	10 (14.7%)	9 (13.4%)	11 (15.3%)
P-value†	0.623				

† Fisher's exact test or Chi-square test.
§ One-way Analysis of Variance.
SAF: Safety Analysis Set; T2DM: type 2 diabetes mellitus
Source: Table 12.1.3.1.1

In addition, treatment groups were comparable in terms of baseline HbA_{1c} (%) and FPG (mg/dL) (Table 3).

Table 3 Baseline Efficacy Variables – SAF

Parameter	Placebo	Ipragliflozin			
		12.5 mg qd	50 mg qd	150 mg qd	300 mg qd
	n=66	n=69	n=68	n=67	n=72
HbA_{1c} (%)					
n	66	69	68	67	72
Mean	7.68	7.78	7.76	7.73	7.87
SD	0.60	0.64	0.66	0.69	0.82
Min	6.8	6.7	6.7	6.5	6.7
Median	7.55	7.70	7.70	7.70	7.70
Max	8.9	9.3	9.0	9.9	11.6
P-value†	0.585				
HbA_{1c} (%)					
<8.0%	45 (68.2%)	41 (59.4%)	43 (63.2%)	45 (67.2%)	45 (62.5%)
≥8.0%	21 (31.8%)	28 (40.6%)	25 (36.8%)	22 (32.8%)	27 (37.5%)
P-value‡	0.825				
FPG (mg/dL)					
n	66	69	68	67	72
Mean	154.8	157.9	153.9	151.6	157.5
SD	27.7	41.3	35.3	30.6	38.5
Min	102	96	62	90	92
Median	151.0	154.1	148.9	147.9	151.0
Max	242	300	259	286	331
P-value†	0.820				

† One-way Analysis of Variance.
‡ Fisher's exact test or Chi-square test.
FPG: fasting plasma glucose; HbA_{1c}: glycated hemoglobin; SAF: Safety Analysis Set.
Source: Table 12.1.3.3.1

Efficacy Results:

Primary Efficacy Variable

The analysis of the primary efficacy variable (% HbA_{1c}), showed a dose-dependent and statistically significant ($P < 0.05$ for all comparisons) decrease for all ipragliflozin doses in change from baseline to end of treatment (week 12 LOCF) compared with placebo (Table 4). The mean decreases in HbA_{1c} corrected for placebo from baseline to week 12 LOCF were -0.22%, -0.34%, -0.40% and -0.48% for ipragliflozin 12.5, 50, 150 and 300 mg respectively.

Table 4 Change from Baseline in HbA_{1c} to End of Treatment (Week 12 LOCF) – Inferential Statistics – FAS

Statistic	Placebo	Ipragliflozin			
		12.5 mg qd	50 mg qd	150 mg qd	300 mg qd
	n=65	n=69	n=66	n=66	n=71
n	65	69	66	66	71
LS mean (%)	-0.31	-0.53	-0.65	-0.72	-0.79
95% CI of LS mean	-0.50, -0.13	-0.71, -0.36	-0.83, -0.47	-0.90, -0.53	-0.97, -0.62
LS mean difference (%)		-0.22	-0.34	-0.40	-0.48
95% CI †		-0.42, -0.02	-0.54, -0.14	-0.60, -0.20	-0.68, -0.27
P-value†		0.033	0.001	< 0.001	< 0.001

† Pairwise comparisons with placebo, using the one-way ANCOVA (with baseline HbA_{1C} as a covariate and treatment group as fixed effects and site as a random effect)
ANCOVA: Analysis of Covariance; FAS: Full Analysis Set; HbA_{1c}: glycated hemoglobin; LOCF: Last Observation Carried Forward; LS: Least Squares.
Source: Table 12.3.1.2

Secondary Efficacy Variables

For change in FPG (mg/dL) from baseline to end of treatment (week 12 LOCF), all pairwise comparisons with placebo were statistically significant for the ipragliflozin 50 mg dose and higher ($P \leq 0.008$) (Table 5).

Table 5 Change from Baseline in FPG (mg/dL) to End of Treatment (Week 12 LOCF) – Inferential Statistics - FAS

Statistic	Placebo	Ipragliflozin			
		12.5 mg qd	50 mg qd	150 mg qd	300 mg qd
	n=65	n=69	n=66	n=66	n=71
n	65	69	66	66	71
LS mean (mg/dL)	-1.0	-8.5	-14.3	-24.3	-27.8
95% CI of LS mean	-8.8, 6.8	-16.1, -0.9	-22.0, -6.6	-32.1, -16.5	-35.3, -20.3
LS mean difference (mg/dL)		-7.5	-13.3	-23.3	-26.8
95% CI †		-17.2, 2.3	-23.0, -3.5	-33.1, -13.5	-36.5, -17.1
P-value†		0.132	0.008	< 0.001	< 0.001

† Pairwise comparisons with placebo, using the one-way ANCOVA (with baseline HbA_{1C} as a covariate and treatment group as fixed effects and site as a random effect).
ANCOVA: Analysis of Covariance; FAS: Full Analysis Set; FPG: fasting plasma glucose; LOCF: Last Observation Carried Forward; LS: Least Squares.
Source: Table 12.3.5.2.1

For the FAS population, there was a statistically significant difference in the proportion of patients achieving $HbA_{1c} < 7.0\%$ (although not for $HbA_{1c} < 6.5\%$) at week12 LOCF between placebo and ipragliflozin groups (Table 6).

Table 6 Proportion of Patients Achieving Glucose Control as Measured by HbA_{1c} to End of Treatment (Week 12 LOCF) - FAS

Glucose Control at Week 12 LOCF ‡	Placebo	Ipragliflozin				P-value†
		12.5 mg qd	50 mg qd	150 mg qd	300 mg qd	
	n=65	n=69	n=66	n=66	n=71	
	n (%)	n (%)	n (%)	n (%)	n (%)	
HbA_{1c} < 7.0%	22 (33.8%)	23 (33.3%)	36 (54.5%)	35 (53.0%)	37 (52.1%)	0.003
HbA_{1c} < 6.5%	9 (13.8%)	8 (11.6%)	11 (16.7%)	12 (18.2%)	17 (23.9%)	0.059

† Cochran-Armitage test for trend.

‡ If no post-baseline value was available patient was counted as failure to achieve glucose control.
FAS: Full Analysis Set; HbA_{1c}: glycated hemoglobin; LOCF : last observation carried forward.
Source: Table 12.3.7.1

Safety Results:

In total, 26 (39.4%), 31 (44.9%), 27 (39.7%), 31 (46.3%) and 37 (51.4%) patients in the placebo and ipragliflozin 12.5 mg, 50 mg, 150 mg and 300 mg dose groups, respectively, experienced a TEAE (Table 7).

Table 7 Incidence of Treatment-Emergent Adverse Events Experienced by at least 5% patients in Any Treatment Arm (MedDRA v12.1) - SAF

MedDRA (v12.1) System Organ Class Preferred Term	Placebo	Ipragliflozin			
		12.5 mg qd	50 mg qd	150 mg qd	300 mg qd
	n=66	n=69	n=68	n=67	n=72
All Systems	26 (39.4%)	31 (44.9%)	27 (39.7%)	31 (46.3%)	37 (51.4%)
Infections and Infestations	10 (15.2%)	10 (14.5%)	8 (11.8%)	15 (22.4%)	15 (20.8%)
Nasopharyngitis	3 (4.5%)	2 (2.9%)	2 (2.9%)	5 (7.5%)	2 (2.8%)
Urinary tract infection	4 (6.1%)	1 (1.4%)	2 (2.9%)	3 (4.5%)	4 (5.6%)
Influenza	0	1 (1.4%)	1 (1.5%)	1 (1.5%)	4 (5.6%)
Gastrointestinal Disorders	6 (9.1%)	12 (17.4%)	5 (7.4%)	10 (14.9%)	6 (8.3%)
Diarrhoea	5 (7.6%)	4 (5.8%)	0	2 (3.0%)	3 (4.2%)
Constipation	0	2 (2.9%)	0	4 (6.0%)	1 (1.4%)
Investigations	4 (6.1%)	1 (1.4%)	5 (7.4%)	6 (9.0%)	7 (9.7%)
Blood glucose increased	1 (1.5%)	0	2 (2.9%)	3 (4.5%)	4 (5.6%)
Renal and Urinary Disorders	1 (1.5%)	5 (7.2%)	6 (8.8%)	4 (6.0%)	4 (5.6%)
Nervous System Disorders	2 (3.0%)	3 (4.3%)	4 (5.9%)	5 (7.5%)	5 (6.9%)
Headache	1 (1.5%)	3 (4.3%)	2 (2.9%)	1 (1.5%)	4 (5.6%)
Metabolism and Nutrition Disorders	5 (7.6%)	1 (1.4%)	5 (7.4%)	3 (4.5%)	2 (2.8%)
General Disorders and Administration Site Conditions	0	2 (2.9%)	4 (5.9%)	5 (7.5%)	3 (4.2%)
Injury, Poisoning and Procedural Complications	2 (3.0%)	1 (1.4%)	0	0	4 (5.6%)

Source: Table 12.6.1.2

The most commonly experienced TEAEs by SOC were 'Infections and Infestations' and 'Gastrointestinal Disorders'. Overall, individual TEAEs were distributed at a similar incidence across the treatment groups and there was no indication of a dose-dependency in these events.

TEAEs of pollakiuria, constipation, and thirst were present in the ipragliflozin dose groups but not in the placebo group. Although these TEAEs were reported in the ipragliflozin dose groups, there was no indication of a dose-dependency in these events.

Most TEAEs were of mild or moderate severity in all treatment groups.

The proportion of patients with drug-related TEAEs was greater in the ipragliflozin dose groups compared with the placebo group. The proportion of patients experiencing TEAEs leading to permanent discontinuation and drug-related TEAEs leading to permanent discontinuation was greater in the placebo group than the ipragliflozin dose groups.

Overall, there were few AEs of special interest in any treatment group (Table 8).

Table 8 Overview of Incidence of TEAEs – SAF

Incidence of:	**Placebo**	**Ipragliflozin**			
		12.5 mg qd	**50 mg qd**	**150 mg qd**	**300 mg qd**
	n=66	n=69	n=68	n=67	n=72
Adverse events	26 (39.4%)	31 (44.9%)	27 (39.7%)	31 (46.3%)	37 (51.4%)
Drug-related †adverse events	7 (10.6%)	11 (15.9%)	11 (16.2%)	14 (20.9%)	10 (13.9%)
Deaths	0	0	0	0	0
SAEs	0	0	1 (1.5%)	0	1 (1.4%)
Drug-related † SAEs	0	0	1 (1.5%)	0	0
Adverse events leading to permanent discontinuation of study drug	3 (4.5%)	2 (2.9%)	1 (1.5%)	1 (1.5%)	0
Drug related adverse events leading to permanent discontinuation of study drug	3 (4.5%)	2 (2.9%)	1 (1.5%)	0	0
Adverse events of special interest					
Hypoglycemia	2 (3.0%)	0	4 (5.9%)	3 (4.5%)	2 (2.8%)
Urinary tract infection	4 (6.1%)	1 (1.4%)	2 (2.9%)	4 (6.0%)	5 (6.9%)
Genital infection	1 (1.5%)	3 (4.3%)	0	2 (3.0%)	0

† Possible or probable, as assessed by the investigator, or records where the relationship was missing.
SAE; Serious Adverse Event; SAF: Safety Analysis Set; TEAE: Treatment Emergent Adverse Event.
Source: Table 12.6.1.1

Treatment emergent hypoglycemia occurred infrequently without a clear dose relationship, was mostly asymptomatic, and recovered in all but one case the same day without medical intervention. None of the hypoglycemic events was persistent, resulted in hypoglycemic coma, required hospitalization or required discontinuation of study drug.

Urinary tract infections occurred infrequently.

GTIs were reported relatively infrequently in this study. In general, GTIs recovered with standard antifungal treatment without interruption of study drug. No events of recurrent infections after recovery were reported nor any other complications.

Skin rash or urticaria was reported in 4 patients one in each of the ipragliflozin groups. One event required discontinuation of study drug in addition to treatment. No severe or complicated skin abnormalities were reported.

There were no deaths during the study.

Two treatment emergent SAEs were reported. One patient in the ipragliflozin 50 mg group experienced treatment-emergent renal impairment; this SAE was considered probably related to the study medication by the investigator. One patient in the ipragliflozin 300 mg group experienced treatment-emergent depression and a panic attack which were not considered to be related to the study medication.

For laboratory mean values, small increases in hemoglobin and hematocrit were observed from baseline to week 12. However, the changes were slight and tended to return to the pre-dose values after the end of study treatment. With the exception of small mean clinically not relevant increases in magnesium, which remained within the normal range, no changes in blood electrolytes were observed in the ipragliflozin groups over the 12 week study. There was a tendency towards a decrease in mean values from baseline to week 12 in the ipragliflozin groups compared with placebo for alkaline phosphatase, ALT, AST, GGT and uric acid.
For urinalysis, small changes in urinary sodium were noticed in the ipragliflozin groups. Across the treatment groups, there was no apparent trend in mean changes from baseline to week 12 in serum lipids.
No apparent trend in changes from baseline to week 12 were observed in mean values for serum or urinary creatinine, total protein, urinary alpha 1 MIC, urinary beta 2 MIC, urinary NAG and eGFR (MDRD and Cockcroft-Gault). There was a tendency towards an increase in mean values for BUN/creatinine ratio from baseline to week 12 in all treatment groups.
For bone markers, a tendency towards an increase in values was observed in the ipragliflozin groups for serum C –terminal crosslinking telopeptide and urinary N-terminal X-linking telopeptide/creatinine

There were no reports of liver toxicity. The incidence of patients with increased liver enzymes was small in all treatment groups.

There were no notable changes in ECG results from baseline to week 12.

CONCLUSIONS:

- In the primary analysis of the primary efficacy variable, there were dose-dependent and statistically significant ($P < 0.05$) decreases for all ipragliflozin doses in change from baseline HbA_{1c} to end of treatment (week 12 LOCF) compared with placebo. The mean decreases in HbA_{1c} corrected for placebo from baseline to week 12 LOCF were -0.22%, -0.34%, -0.40% and -0.48% for ipragliflozin 12.5, 50, 150 and 300 mg respectively.

- For the secondary efficacy variable, dose-dependent and statistically significant decreases in FPG (mg/dL) from baseline to end of treatment (Week 12) were shown for ipragliflozin 50 mg dose and higher, compared with placebo.
- For the FAS population, there was a statistically significant difference in the proportion of patients achieving $HbA_{1c} < 7.0\%$ (although not for $HbA_{1c} < 6.5\%$) at week12 LOCF between placebo and ipragliflozin groups.
- Ipragliflozin in doses of 12.5, 50, 150 and 300 mg (qd) for 12 weeks was safe and well tolerated.
- Based on benefit/risk assessment, this dose-finding study supports the use of ipragliflozin dosages of 50 mg and higher for further development in patients with T2DM.

Date of Report: Reissued, 25 November 2014