

Name of Sponsor/Company: Astellas Pharma Global Development, Inc. (APGD-US)		
Name of Finished Product: Ipragliflozin		
Name of Active Ingredient: Ipragliflozin (ASP1941)		

SYNOPSIS

Title of Study: A Phase 2, Double-Blind, Randomized, Placebo and Active-Controlled Dose-Finding Study to Assess the Efficacy, Safety and Tolerability of Multiple Oral Doses of ASP1941 in Patients with Type 2 Diabetes Mellitus.

Investigators/Coordinating Investigator:

[redacted] MD, [redacted], United States of America (USA)

Study Centers:

A total of 59 sites were initiated in the USA, Mexico, Colombia, India and the Philippines.

Publication (reference):

None

Study Period:

The treatment period was 12 weeks, preceded by a 2-week placebo run-in period and a 6-week washout period if required. Patients were followed up for 4 weeks after the end of treatment.

Date of first enrollment (Study initiation date):

03 March 2010

Date of last evaluation (Study completion date):

11 April 2011

Phase of Development:

Phase 2

Objectives:

The primary objective of the study was to evaluate the efficacy of 4 doses of ipragliflozin over 12 weeks of therapy in male and female patients with type 2 diabetes mellitus (T2DM).

Secondary objectives were to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of ipragliflozin in the target population.

Methodology:

This was a 12-week multi-center, double-blind, double-dummy, randomized, parallel group, placebo and active-controlled, multiple-dose study in patients with T2DM.

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Patients were stratified at randomization (visit 4) into 2 strata based on whether they required washout of previous anti-diabetic medication (entry at visit 1) or were drug naïve (entry at visit 3). Patients were randomized 1:1:1:1:1:1 to 1 of 4 active ipragliflozin treatment groups, placebo, or metformin. The metformin group was added as reference, and the study was not designed to do formal comparisons between ipragliflozin and metformin, or placebo and metformin.

Patients currently taking oral anti-diabetic medication were required to undergo a 6-week washout period followed by a 2-week placebo run-in before entering the 12-week treatment period. Patients who were naïve to anti-diabetic medication (for at least 6 weeks) entered directly into the 2-week placebo run-in period. Blood glucose was assessed periodically during the washout, placebo run-in, treatment and follow-up periods to assess glycemic control. All patients were followed for 4 weeks after study treatment had been discontinued.

Patients in the metformin arm were initiated on metformin at a dose of 1000 mg per day which was increased to 1500 mg per day after 2 weeks.

Number of Patients (planned, enrolled and analyzed):

It was planned that 378 patients (63 patients in each treatment group) would be enrolled at approximately 80 sites. In total 1035 patients were screened, 670 were enrolled in the run-in period, 412 were randomized to treatment and 363 (88.1% of randomized patients) completed the 12-week study. See flow diagram in [Figure 1].

Diagnosis and Main Criteria for Inclusion:

Male or female patients aged 18 years or older, diagnosed with T2DM for at least 6 weeks, with a glycated hemoglobin (HbA_{1c}) value between 6.8 and 9.5% at visit 1 and a HbA_{1c} value between 7.0 and 9.5%, inclusive, at visit 3, were eligible for inclusion in this study. Eligible patients must also have been naïve to anti-diabetic medication; or have been receiving a single anti-diabetic agent or low dose of a dual oral combination therapy ($\leq$ 50% of maximum doses of each component), and have been willing and able to safely discontinue anti-diabetic therapy at screening. Eligible patients must also have provided written informed consent for study participation, and fulfilled none of the study exclusion criteria.

All non-study anti-diabetic medications were strictly prohibited during the study (through visit 10).

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

Ipragliflozin was administered as oral tablets containing 12.5 mg and 50 mg ipragliflozin L-proline, as the free base and had an OPADRY® OY-S-32954 yellow film-coating. Patients received ipragliflozin or placebo-to-match (PTM) for 12 weeks. All patients took 7 ipragliflozin or PTM tablets once daily in the morning with breakfast [Table 1].

Table 1 Tablet and Capsule Breakdown by Dose Group

	Blister Packs					
	Ipragliflozin				Metformin	
	12.5 mg	PTM 12.5 mg	50 mg	PTM 50 mg	500 mg	PTM
First 2 Weeks of Treatment Period						
Group 1: Ipragliflozin 12.5 mg	1	None	None	6	None	2
Group 2: Ipragliflozin 50 mg	None	1	1	5	None	2
Group 3: Ipragliflozin 150 mg	None	1	3	3	None	2
Group 4: Ipragliflozin 300 mg	None	1	6	None	None	2
Group 5: Metformin 1000 mg	None	1	None	6	2	None
Group 6: Placebo	None	1	None	6	None	2
Following 10 Weeks of Treatment Period						
Group 1: Ipragliflozin 12.5 mg	1	None	None	6	None	3
Group 2: Ipragliflozin 50 mg	None	1	1	5	None	3
Group 3: Ipragliflozin 150 mg	None	1	3	3	None	3
Group 4: Ipragliflozin 300 mg	None	1	6	None	None	3
Group 5: Metformin 1500 mg	None	1	None	6	3	None
Group 6: Placebo	None	1	None	6	None	3

PTM: Placebo to match

Batch Numbers – Test Product

Ipragliflozin 12.5 mg batch number: [redacted]

Ipragliflozin 50 mg batch numbers: [redacted], [redacted] [redacted]

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

Placebo run-in: Patients received a 2-week placebo run-in prior to being randomized to a treatment regimen.

Treatment period: Patients received double-blind, double-dummy study treatment for 12 weeks, as detailed in [Table 1].

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

Metformin was administered as over-encapsulated capsules containing metformin hydrochloride 500 mg tablets.

First 2 weeks of randomized treatment: Patients assigned to metformin began taking 1000 mg each day for 2 weeks (500 mg in the morning and 500 mg in the evening). All patients took two 2 metformin or metformin placebo capsules from blistered wallet cards each day [Table 1].

Remaining 10 weeks of randomized treatment: Patients assigned to the metformin group were increased to 1500 mg (500 mg in the morning and 1000 mg in the evening). All patients took three 3 metformin or metformin placebo capsules from blistered wallet cards each day: one 1 in the morning with breakfast and two 2 in the evening with dinner [Table 1].

Batch numbers – Reference Products

Metformin 500 mg batch numbers: [redacted]

Metformin PTM 500 mg batch numbers: [redacted]

Ipragliflozin PTM 12.5 mg batch numbers: [redacted]

Ipragliflozin PTM 50 mg batch numbers: [redacted]

Criteria for Evaluation:

The primary efficacy analysis was:

- Change from baseline (visit 4) to week 12 in HbA_{1c}

Secondary efficacy variables included:

- Change from baseline in fasting plasma glucose (FPG) at week 12
- Proportion of patients who achieved a target goal ($HbA_{1c} < 7.0\%$) at week 12
- Proportion of patients who achieved a target goal ($HbA_{1c} < 6.5\%$) at week 12

Analysis of exploratory efficacy variables included the following:

- [redacted]

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- [redacted]
- [redacted]

Analysis of other efficacy variables included:

- Change from baseline in health outcomes at week 12 as measured by the following patient-reported outcome (PRO) questionnaires:
    - EuroQol Group health outcome measure (EQ-5D)
    - Audit of Diabetes-Dependent Quality of Life (ADDQoL)
    - Diabetes Medication Satisfaction (Diab-MedSat)

Plasma levels of ipragliflozin and metformin were taken for population pharmacokinetic analysis. The pharmacokinetic/pharmacodynamic results will be reported in a separate document.

Safety was assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs)
- Physical examinations
- Clinical laboratory assessments
- Vital signs
- 12-lead electrocardiogram (ECG) measurements

Statistical Methods:

For the analysis of the primary variable, changes in HbA_{1c} were compared using analysis of covariance (ANCOVA) with baseline HbA_{1c} as the covariate, treatment group and prior anti-diabetic medication (randomization strata) 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. Where necessary, a pooling algorithm was to be determined and documented prior to hardlock and unblinding. Pairwise comparisons to 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.

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Interactions with treatment were examined and, if significant, were included in a secondary analysis. Pairwise comparisons between metformin and each ipragliflozin group and between metformin and placebo were also evaluated as secondary analyses. [redacted]

Analyses of secondary variables: To compare changes in FPG, ANCOVA was used with baseline FPG as the covariate, treatment group and prior anti-diabetic medication (randomization strata) as fixed effects, and site as a random effect. LOCF was used in the primary analysis and actual data were used in a secondary analysis. Pairwise comparisons between placebo and each ipragliflozin group were performed. Pairwise comparisons between metformin and each ipragliflozin group and between metformin and placebo may also have been evaluated.

Analysis of additional secondary variables included the following:

- Proportion of patients who achieved a target goal ($HbA_{1c} < 7.0\%$) at week 12
- Proportion of patients who achieved a target goal ($HbA_{1c} < 6.5\%$) at week 12

The Cochran-Armitage test for trend was applied to the proportion of patients who achieved a target goal ($HbA_{1c} < 7.0\%$ or $< 6.5\%$) at week 12 in each of the ipragliflozin doses compared to placebo. LOCF was used in the primary analysis at week 12 and actual data were used in secondary analyses at each visit.

Summary of Results/Conclusions:

Population

The patient disposition is summarized in the flow diagram in [Figure 1].

There was no statistically significant difference between ipragliflozin treatment groups and placebo in terms of gender, race or age [Table 12.1.3.1.1]. Approximately half of the patients were white and the majority were ≤ 65 years of age.

In terms of baseline characteristics, there was no statistically significant difference between ipragliflozin treatment groups and placebo in terms of years since diagnosis of T2DM, weight, body mass index (BMI), waist circumference or waist/hip ratio [Table 12.1.3.2.1]. However, the difference amongst all ipragliflozin treatment groups and placebo in term of height was statistically significant (P = 0.027), but not clinically relevant.

Most patients had been diagnosed with T2DM within the previous 10 years and the mean time since diagnosis across the groups ranged from 4.08 to 5.11 years [Table 12.1.3.2.1].

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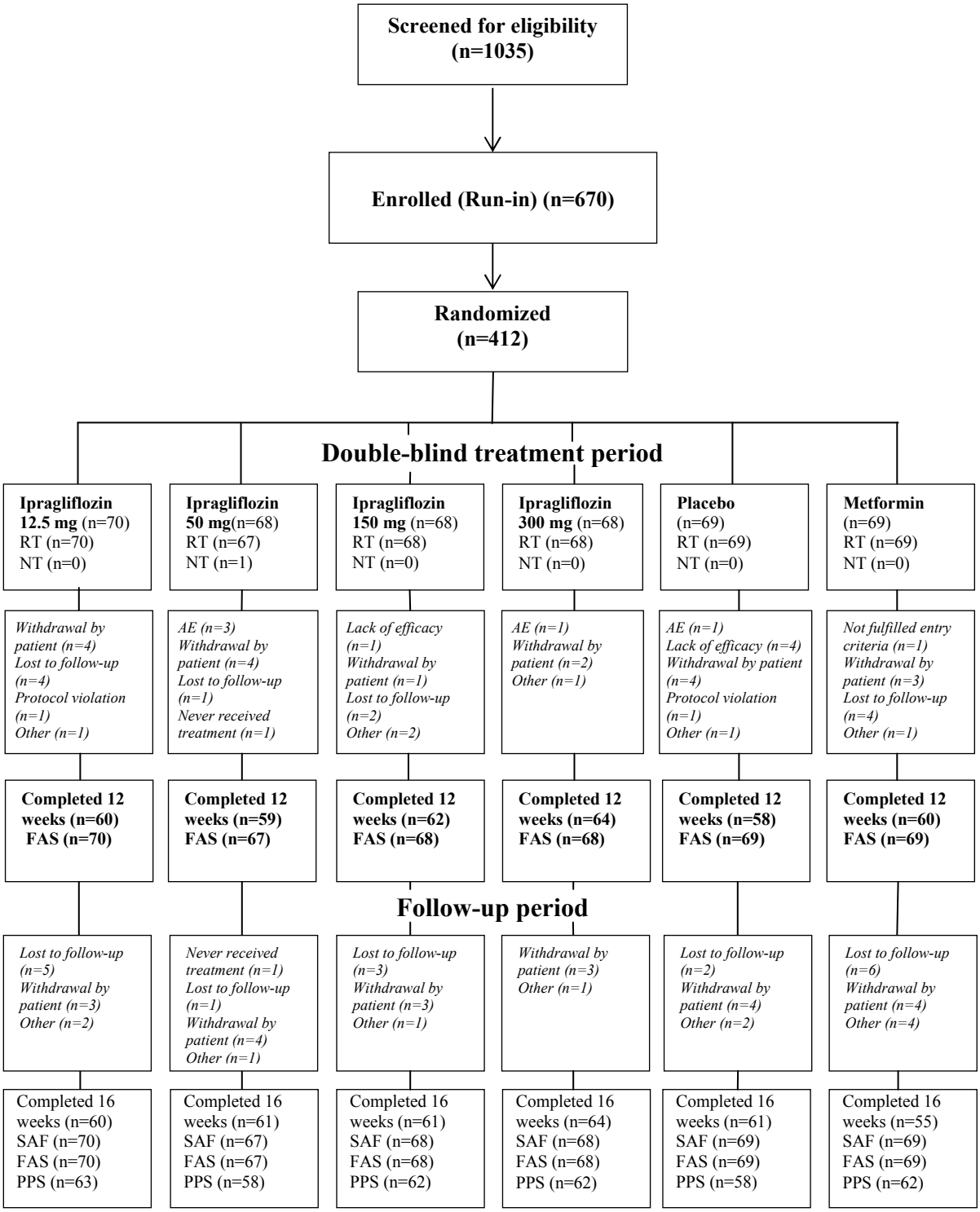
There was no statistically significant difference between treatment groups in terms of baseline HbA_{1c} (%) or FPG (mg/dL) [Table 12.1.3.3.1]. Mean HbA_{1c} (%) baseline values ranged between 7.83% and 8.05%. Correspondingly, at least 50.0% of patients in each treatment group had < 8.0% HbA_{1c}. Mean FPG (mg/dL) baseline values ranged between 160.3 mg/dL (ipragliflozin 300 mg) to 169.6 mg/dL (metformin).

Figure 1 Patient Disposition



Note: Only the primary reason for discontinuation for each patient is summarized.
AE: adverse event; FAS: Full Analysis Set; NT: not treated; RT: Received treatment; PPS: Per-Protocol Set; SAF: Safety Analysis Set
Source: Tables 12.1.1.1, 12.1.1.2, 12.1.2.1, and 12.1.2.2

Efficacy/Pharmacokinetic/Pharmacodynamic Results:

Primary Efficacy Variable

Pairwise comparisons with placebo of the LS mean decreases from baseline in HbA_{1c} at week 12 were statistically significant for all ipragliflozin dose groups ($P < 0.001$) with adjustment for baseline HbA_{1c}, prior anti-diabetic medication and study site. The LS mean differences from placebo at week 12 (LOCF data) showed dose-dependent decreases from baseline in HbA_{1c} across the ipragliflozin dose groups [Table 2]. [redacted]

Table 2 Change from Baseline in HbA_{1c} to End of Treatment (Week 12 LOCF) – Inferential Statistics – FAS

Statistic	Placebo	Ipragliflozin				[redacted]
		12.5 mg	50 mg	150 mg	300 mg	
	n = 69	n = 70	n = 67	n = 68	n = 68	
n	69	70	66	66	68	
LS mean	0.26	-0.22	-0.39	-0.47	-0.55	
95% CI of LS mean	0.08; 0.45	-0.41,-0.04	-0.58, -0.20	-0.66, -0.27	-0.73, -0.36	
LS mean difference†	-	-0.49	-0.65	-0.73	-0.81	
P-value	-	< 0.001	< 0.001	< 0.001	< 0.001	
95% CI	-	-0.73, -0.24	-0.90, -0.40	-0.98, -0.48	-1.06,-0.56	
n	-	-	-	-	-	
LS mean difference‡	-	-	-	-	-	
P-value	-	-	-	-	-	
95% CI	-	-	-	-	-	
LS mean difference§	-	0.24	0.08	0	-0.08	
P-value	-	0.057	0.521	0.977	0.539	
95% CI	-	-0.01, 0.49	-0.17, 0.33	-0.25, 0.26	-0.33, 0.17	

[redacted]

- : not applicable; ANCOVA: analysis of covariance; FAS: Full Analysis Set; HbA_{1c}: glycated hemoglobin; LOCF; last observation carried forward; LS: least square
† Pairwise comparisons between each ipragliflozin dose group and placebo, using the one-way ANCOVA with the same 'n' as for the overall model.
‡ Pairwise comparisons between metformin and placebo, using the one-way ANCOVA with all treatment groups.
§ Pairwise comparisons between each ipragliflozin dose group and metformin, using the one-way ANCOVA with all treatment groups.
Source: Table 12.3.1.2

Secondary Efficacy Variables

There were statistically significant changes from baseline in FPG (mg/dL) from baseline to the end of treatment (week 12) for all pairwise comparisons of ipragliflozin dose groups with placebo ($P = 0.005$ and $P < 0.001$ for pairwise comparisons between placebo and ipragliflozin 12.5 mg and all other ipragliflozin dose groups, respectively), with adjustments for baseline FPG, prior anti-diabetic medication and study site [Table 3].

Table 3 Change from Baseline in FPG to End of Treatment (Week 12 LOCF) – Inferential Statistics – FAS

Statistic	Placebo	Ipragliflozin				[redacted]
		12.5 mg	50 mg	150 mg	300 mg	
	n = 69	n = 70	n = 67	n = 68	n = 68	
n	69	70	66	68	68	
LS mean	-0.2	-15.4	-20.0	-23.6	-30.5	
95% CI of LS mean	-8.0, 7.5	-23.1, -7.6	-27.9, -12.1	-31.4, -15.8	-38.3, -22.6	
LS mean difference†	-	-15.1	-19.8	-23.4	-30.3	
P-value	-	0.005	< 0.001	< 0.001	< 0.001	
95% CI	-	-25.6, -4.7	-30.4, -9.1	-33.9, -12.9	-40.8, -19.7	
n	-	-	-	-	-	
LS mean difference‡	-	-	-	-	-	
P-value	-	-	-	-	-	
95% CI	-	-	-	-	-	
LS mean difference§	-	5.5	1.3	-2.4	-9.3	
P-value	-	0.309	0.816	0.658	0.089	
95% CI	-	-5.2, 16.2	-9.5, 12.1	-13.2, 8.4	-20.1, 1.4	

[redacted]

- : not applicable; ANCOVA: analysis of covariance; FAS: Full Analysis Set; FPG: fasting plasma glucose; LOCF: last observation carried forward; LS: least square
† Pairwise comparisons between each ipragliflozin dose group and placebo, using the one-way ANCOVA with the same 'n' as for the overall model.
‡ Pairwise comparisons between metformin and placebo, using the one-way ANCOVA with all treatment groups.
§ Pairwise comparisons between each ipragliflozin dose group and metformin, using the one-way ANCOVA with all treatment groups.
Source: Table 12.3.5.2.1

There was a statistically significant (P = 0.002) difference between placebo and ipragliflozin in the proportion of patients achieving glucose control as measured by HbA_{1c} < 7.0% at week 12 (LOCF data) [Table 4], but no significant difference between treatment groups for patients achieving HbA_{1c} < 6.5% at week 12 (LOCF data) [Table 4].

Table 4 Proportion of Patients Achieving Glucose Control as Measured by HbA_{1c} at End of Treatment (Week 12 LOCF) – FAS

Glucose Control‡	Placebo	Ipragliflozin				P-value†	Metformin
		12.5 mg	50 mg	150 mg	300 mg		
	n = 69	n = 70	n = 67	n = 68	n = 68	-	n = 69
	n (%)	n (%)	n (%)	n (%)	n (%)	-	n (%)
HbA_{1c} < 7.0 %	10 (14.5)	14 (20.0)	15 (22.4)	16 (23.5)	26 (38.2)	0.002	24 (34.8)
HbA_{1c} < 6.5 %	5 (7.2)	4 (5.7)	4 (6.0)	6 (8.8)	7 (10.3)	0.364	10 (14.5)

- : not applicable; FAS: Full Analysis Set; HbA_{1c}: glycated hemoglobin; LOCF: last observation carried forward
† Cochran-Armitage test for trend, for ipragliflozin dose groups and placebo.
‡ If no post-baseline value was available patient was counted as failure to achieve glucose control.
Source: Table 12.3.7.1

Safety Results:

Drug-related TEAEs were reported by patients in all treatment groups, with the highest proportions of patients experiencing at least 1 drug-related TEAE occurring in the ipragliflozin 50 mg and placebo groups (25.4% and 24.6%, respectively).

In total 7 patients permanently discontinued the study as a result of AEs, and 5 patients discontinued due to drug-related AEs, with the highest number in both cases being from the ipragliflozin 50 mg dose group (3 patients; 4.5%).

The most commonly reported TEAEs by SOC were 'Infections and infestations' (primarily urinary tract infections) and 'Gastrointestinal disorders', followed by 'Vascular disorders' (primarily hypertension). There was no indication that the frequency of these TEAEs was related to the dose of ipragliflozin [Table 5]. There was no indication that the incidences of any specific AEs (by preferred term) were greater in the ipragliflozin dose groups than the placebo or metformin groups.

Table 5 Incidence of TEAEs Experienced by at Least 5% patients in Any Treatment Arm (MedDRA v12.1) – SAF

Primary system organ class Preferred term	Placebo	Ipragliflozin				Metformin
		12.5 mg	50 mg	150 mg	300 mg	
	n = 69	n = 70	n = 67	n = 68	n = 68	n = 69
All systems	43 (62.3%)	32 (45.7%)	36 (53.7%)	33 (48.5%)	40 (58.8%)	41 (59.4%)
Infections and infestations	13 (18.8%)	10 (14.3%)	18 (26.9%)	10 (14.7%)	18 (26.5%)	13 (18.8%)
Urinary tract infection	6 (8.7%)	4 (5.7%)	8 (11.9%)	1 (1.5%)	5 (7.4%)	5 (7.2%)
Nasopharyngitis	2 (2.9%)	0	2 (3.0%)	2 (2.9%)	4 (5.9%)	1 (1.4%)
Gastrointestinal disorders	13 (18.8%)	9 (12.9%)	9 (13.4%)	6 (8.8%)	11 (16.2%)	14 (20.3%)
Diarrhea	3 (4.3%)	1 (1.4%)	2 (3.0%)	2 (2.9%)	3 (4.4%)	7 (10.1%)
Vascular disorders	3 (4.3%)	3 (4.3%)	1 (1.5%)	2 (2.9%)	1 (1.5%)	4 (5.8%)
Hypertension	3 (4.3%)	2 (2.9%)	1 (1.5%)	0	0	4 (5.8%)

SAF: Safety Analysis Set; TEAE: treatment-emergent adverse event
Source: Table 12.6.1.2

Regarding TEAEs of special interest, 2 patients (1 in each of the ipragliflozin 50 mg and 300 mg dose groups) experienced treatment-emergent hypoglycemia [Table 6]. None of the hypoglycemic events required medical intervention and both patients completed the double-blind treatment phase without interruption of study drug.

Urinary tract infections (UTI) overall (as classified by the investigator) was the most commonly reported TEAE of special interest by SOC and were reported by a total of 32 patients (42 events) across all treatment groups [Table 6]. UTIs were reported by 1 (1.5%) to 9 (13.4%) patients across the ipragliflozin treatment groups, 6 (8.7%) patients in the placebo group and 5 (7.2%) patients in the metformin group. UTIs were more than twice as frequent in women (22 patients) as men (10 patients). There was no indication that the frequency of any of UTIs was related to the dose of ipragliflozin in either gender. None of the UTIs resulted in hospitalization or in complications such as urosepsis or renal impairment.

A total of 14 patients experienced treatment-emergent genital infections (18 events) [Table 6]. Treatment-emergent genital infections were reported in all treatment groups except the ipragliflozin 12.5 mg dose group and were most frequently reported in the-ipragliflozin 50 mg dose group (8 patients). The incidence of genital infections was higher in women than in men. Of the 6 events reported in male patients, 4 were reported by a single site in India. The reported genital infections represented a heterogeneous group of diseases that were reported to be related to a bacterial or a fungal infection. All genital infections responded to a standard first line treatment regimen and no complications were reported. All except 2 events resolved within the treatment period.

Table 6 Incidence of TEAEs of Special Interest (MedDRA v12.1) - SAF

System Organ Class Preferred Term	Placebo	Ipragliflozin				Metformin
		12.5 mg	50 mg	150 mg	300 mg	
	n = 69	n = 70	n = 67	n = 68	n = 68	n = 69
Hypoglycemia overall†	0	0	1 (1.5%)	0	1 (1.5%)	0
Metabolism and nutrition disorders	0	0	1 (1.5%)	0	1 (1.5%)	0
Hypoglycemia	0	0	1 (1.5%)	0	1 (1.5%)	0
Urinary tract infection overall†	6 (8.7%)	4 (5.7%)	9 (13.4%)	1 (1.5%)	7 (10.3%)	5 (7.2%)
Infections and infestations	6 (8.7%)	4 (5.7%)	9 (13.4%)	1 (1.5%)	7 (10.3%)	5 (7.2%)
Urinary tract infection	6 (8.7%)	4 (5.7%)	8 (11.9%)	1 (1.5%)	5 (7.4%)	5 (7.2%)
Urinary tract infection bacterial	0	0	1 (1.5%)	0	2 (2.9%)	0
Escherichia urinary tract infection	0	0	1 (1.5%)	0	0	0
Genital infection overall†	1 (1.4%)	0	8 (11.9%)	1 (1.5%)	2 (2.9%)	2 (2.9%)
Infections and infestations	0	0	5 (7.5%)	1 (1.5%)	2 (2.9%)	1 (1.4%)
Vulvovaginal mycotic infection	0	0	3 (4.5%)	1 (1.5%)	0	0
Genital infection fungal	0	0	1 (1.5%)	0	1 (1.5%)	0
Vaginal infection	0	0	0	0	1 (1.5%)	1 (1.4%)
Genital infection bacterial	0	0	1 (1.5%)	0	0	0
Herpes simplex	0	0	0	1 (1.5%)	0	0
Vaginitis bacterial	0	0	1 (1.5%)	0	0	0
Reproductive system and breast disorders	1 (1.4%)	0	3 (4.5%)	0	0	1 (1.4%)
Balanitis	0	0	2 (3.0%)	0	0	1 (1.4%)
Epididymitis	0	0	1 (1.5%)	0	0	0
Vaginal discharge	1 (1.4%)	0	0	0	0	0
Vulvovaginal pruritus	1 (1.4%)	0	0	0	0	0

SAF: Safety Analysis Set; TEAE: treatment-emergent adverse event
† As classified by the investigator.
Source: Table 12.6.1.13

Skin rashes were heterogeneous, reported infrequently and occurred in all treatment groups. There were 2 rash events that were considered to be probably drug-related disseminated skin rashes in the ipragliflozin group that occurred shortly after introduction of the study drug (source: rash questionnaires for patients [redacted] and [redacted]). Both rashes recovered within a few days after discontinuation of the study drug. No complications of skin abnormalities were reported.

There were no deaths during the study.

A total of 4 patients reported treatment-emergent SAEs; 2 in the placebo group and 1 each in the ipragliflozin 150 mg and metformin groups. The events required in-patient hospitalization, but none was considered to be related to the study drug. A further 4 patients experienced SAEs during the screening period or during the follow-up period.

A [redacted] patient was already 22 weeks pregnant when she was randomized to ipragliflozin 50 mg; she completed the study and delivered a healthy newborn.

For laboratory values, there was a tendency towards an increase in hematocrit and hemoglobin 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. There was a tendency towards a decrease in uric acid from baseline to week 12 in the ipragliflozin dose groups compared with placebo. Changes from baseline to week 12 for the other biochemistry parameters tended to be similar across all treatment groups.

Small changes were noticed in some urinary parameters (e.g., sodium), but there were no clinically significant changes from baselines values.

There were no clinically significant changes from baseline values in bone markers, although there was a tendency towards an increase in serum C -terminal crosslinking telopeptide and urinary N-terminal X-linking telopeptide/creatinine ratio in the ipragliflozin treatment groups.

Values for serum lipids tended to be similar across all treatment groups and there were no clinically significant changes from baseline values. For renal parameters there was a tendency towards an increase in the blood urea nitrogen (BUN)/creatinine ratio from baseline to week 12 in the ipragliflozin and metformin dose groups compared with placebo, but no other apparent trend in changes from baseline in renal parameters.

There were no reports of liver toxicity. The incidences of liver enzyme abnormalities were small in all treatment groups.

There were no notable changes from baseline in vital signs or ECG results.

ISN 1941-CL-0004

CONCLUSIONS:

Statistical analyses showed that ipragliflozin provided a dose dependent decrease of HbA_{1c} (primary endpoint) at all doses and FPG (secondary endpoint) at all doses tested over the 12 week study.

Ipragliflozin at doses of 12.5, 50, 150 and 300 mg qd for 12 weeks was found to be safe and well tolerated. The incidence of TEAEs was similar across all treatment groups with no indication of dose dependency.

Overall, there were few AEs of special interest in any treatment group. The most commonly reported TEAEs of special interest by system organ class (SOC) were UTI and genital infection. UTIs and genital infections were both more common in women than men. There was otherwise no evidence that the frequency of UTIs or genital infections was related to dose of ipragliflozin.

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