STUDY REPORT SYNOPSIS

Multi-center, single arm, observational study to evaluate the safety of dapagliflozin in type 2 diabetes mellitus patients in China

Milestones:	Final protocol	10 Nov 2016
	First subject in	16 Aug 2017
	Last subject in	30 Jul 2020
	Data extraction	19 May 2021
	Final statistical analysis report	15 Sep 2021
Phase of development:	IV	
Sponsor:	AstraZeneca Investment (China) Co., Ltd.	

Rationale for this Non-Interventional Study (NIS)

With an increasing prevalence, diabetes casted an enormous challenge to the public health of China with about 114.4 million Chinese adults affected by diabetes in 2017[1], and a large number of patients were inadequately treated and had poor glucose control despite the availability of a wide variety of anti-hyperglycaemia medications[2]. Therefore, a high medical need exists in the management of diabetes in China.

Dapagliflozin is a highly selective sodium-glucose co-transporter 2 (SGLT-2) inhibitor approved for management of hyperglycaemia in adult patients with type 2 diabetes mellitus (T2DM). By inhibiting the activity of SGLT-2 in proximal tubule of kidney, dapagliflozin can significantly reduce renal glucose re-absorption and increase urinary glucose excretion eventually resulting decrease in the level of blood glucose. With this unique mechanism of action (MOA), the effect of dapagliflozin is not dependent on insulin secretion and action. Therefore, the drug could provide potent hyperglycaemia management, which not only meets the patients' needs who aren't well either treated with or tolerate to the existed drugs, but also improves the diabetes care as the MOA is complementary to the existed ones.

Dapagliflozin has been approved for the treatment of T2DM in various countries worldwide, and has been launched in China in Mar 2017, and longer-term safety data have become available. In a pooled study of safety data from 13 global placebo-controlled phase IIb/III clinical trials of dapagliflozin in subjects with T2DM, 60% of subjects (N=2,360) experienced adverse events (AEs), 5.1% experienced serious adverse events (SAEs), 13.7% experienced hypoglycaemia, 4.7% experienced urinary tract infection (UTI), and 5.5% experienced genital tract infection (GTI) [3]. Another pooled analysis conducted in Asian subjects with T2DM from eight phase IIb/III double-blind trials of dapagliflozin showed 56.5%, 53.6% and 58.7% of subjects experienced AEs, 2.8%, 4.1% and 2.4% experienced SAE, 1.4%, 1.6% and 1.9% experienced hypoglycaemia, 4.0%, 3.5% and 4.7% experienced UTI, 0.4%, 1.8% and 2.6% experienced GTI in the placebo group (N=497), dapagliflozin 5 mg group (N=491) and 10 mg group (N=491) [4]. The efficacy and safety profiles in Chinese T2DM subjects were demonstrated in a phase III clinical trial with 396 Asian participants, of whom 89% were Chinese[5]. The results showed AEs occurred in 63.6%, 61.7%, and 60.9% of subjects, SAEs occurred in 1.5%, 3.9%, and 3.0% of subjects, hypoglycaemia occurred in 1.5%, 0.8%, and

0.8% subjects, GTI occurred in 0.8%, 3.1%, and 4.5% of subjects, and UTI occurred in 3.0%, 3.9%, and 5.3% of subjects in the placebo group (N =132), dapagliflozin 5 mg group (N = 128) and 10 mg group (N = 133).

However, more safety evidence on dapagliflozin among Chinese T2DM patients based on large population was highly demanded since the number of patients involved in that trial was limited. Moreover, there was no data to demonstrate the safety and effectiveness of dapagliflozin therapy in Chinese patients with T2DM under real clinical practice setting. It was also required by National Medical Products Administration (NMPA) to assess the newly approved drug in at least 3000 patients within the first five years after commercial launch. Therefore, current study was conducted to demonstrate the safety of dapagliflozin therapy by assessment of the incidence of AEs and SAEs during 6-month follow up in Chinese subjects with T2DM. Meanwhile the exploratory objectives of current study were to describe the change of metabolic factors in T2DM subjects treated with dapagliflozin in real clinical practice measured by change of glycosylated hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), and postprandial plasma glucose (PPG), blood pressure (BP), waist circumference and body weight, and to describe the event-specific incidence of AEs of specific interest (AESI) among Chinese T2DM subjects with dapagliflozin during the study period.

It was anticipated that the data obtained from this post-marketing study would further enhance and supplement the safety data currently available in clinical trials, and this study would provide more detailed information than data obtained through routine spontaneous adverse event reporting.

Objectives of this Non-Interventional Study

Primary objective:

To demonstrate the safety of dapagliflozin by assessment of the incidence of adverse events (AEs) and serious adverse events (SAEs) (especially main AESIs including GTI, UTI, and hypoglycaemia) during 6-month follow up in Chinese subjects with T2DM.

Exploratory objectives:

The exploratory objectives were to describe the change of metabolic factors and incidence of other AESIs in T2DM subjects treated with dapagliflozin when captured in real clinical practice. Metabolic factors included HbA_{1c}, FPG, PPG, body weight, waist circumference, and

BP.

I. To describe glucose control conditions by assessment of the absolute change in HbA_{1c}, FPG, 2-hour postprandial plasma glucose (2h-PPG) and of the proportion of subjects achieving $HbA_{1c} < 7.0\%$ at the end of study;

II. To describe the change of other metabolic factors by assessment of the absolute change in body weight, waist circumference, and blood pressure (systolic and diastolic).

III. To describe the incidence of other AESIs among Chinese T2DM subjects with dapagliflozin during the study period. The other AESIs were volume depletion, abnormal of blood electrolytes, polyuria, renal impairment, diabetic ketoacidosis, hepatic impairment, and hematuria (definition of these events see section 4.3).

Study design

The study is a multi-center, prospective cohort, single arm, observational study performed in 3000 Chinese T2DM subjects recruited from 88 sites of tier 2 or 3 hospitals in China.

Data source

Data were collected from 3000 Chinese T2DM subjects recruited from 88 sites of Chinses tier 2 or 3 hospitals by investigators' inquiry during three face-to-face visits at enrollment (Visit 1), week 12 (Visit 2) and week 24 (Visit 3). If subjects stopped dapagliflozin treatment within the period between Visit 1 and Visit 2, or between Visit 2 and Visit 3, the investigator performed a face-to-face interview or telephone call (if subjects could not come back to hospital) to collect data targeted within 14 days after the investigator noticed or was informed. All AEs/SAEs were documented in case report form (CRF).

Study population

The study enrolled 3000 Chinese subjects who were diagnosed with T2DM and had been initiated the therapy of dapagliflozin by a physician (any licensed physician is qualified) and had taken at least one dose of dapagliflozin in 88 sites of tier 2 or 3 hospitals. The initiation and dosing of dapagliflozin were at the discretion of the physician. No therapy segments were proposed. Any investigator, AstraZeneca (AZ) employee, or contract research organization (CRO) employee must not intervene the decision making of any physician or subject by any path.

Inclusion criteria

The subject population, that were observed in the study, must fulfil all of the following criteria:

I. Provision of subject informed consent prior to any study specific procedures.

II. Chinese, female or male.

III. T2DM diagnosed by physicians according to 2013 Chinese Guideline for Diabetes[6], i.e., 1) Subjects with typical syndrome and with a FPG ≥ 7.0 mmol/L and/or random plasma glucose ≥ 11.1 mmol/L; and/or, 2) subjects without typical syndrome and with repeated FPG ≥ 7.0 mmol/L and/or two hours post challenged plasma glucose ≥ 11.1 mmol/L.

IV. Subjects who already took at least one dose of dapagliflozin, which was prescribed by physicians based on their clinical practice. The prescription of dapagliflozin was separated from the decision to be included in the current study or not.

Exclusion criteria:

Subjects should not enter the study if any of the following exclusion criteria were fulfilled:

I. Being unable to comply with study-specified procedures.

II. Participating in any other clinical trial currently or during the last three months.

III. Previous enrollment in the present study.

Statistical methods

For continuous data, the parameters including mean, standard deviation (SD), medium, minimum, and maximum and for categorical data, the frequency and/or percentage of subjects in each category were calculated and presented. Counts that are zero were displayed as “0”. Percentages were calculated based on non-missing data unless otherwise specified. The 95% confidence interval (CI) would be calculated as appropriate.

The association of subject characteristics with hypoglycaemia, UTI, GTI were explored via Cox proportional hazard model.

Results:

Population characteristics:

A total of 3000 subjects were enrolled from 88 sites, among which 99.7% (2990/3000) was confirmed to have received at least one dose of dapagliflozin to be included in the safety analysis set (SAT). Mean age of subjects was 52.8 years old and male subjects accounted 65.8% of total population. Mean (SD) height, weight and body mass index (BMI) were 167.42 (8.22) cm, 76.09 (13.71) kg and 27.06 (3.85) kg/m^2, respectively. Duration of diabetes for most subjects was less than 20 years (91.4%) with the mean duration being 8.53 years and more than half subjects (59.0%) had a history of diabetes mellitus complications. Most subjects (92.3%) experienced at least one medical history besides T2DM with high incidence in terms of system organ class (SOC): metabolism and nutrition disorders (64.1%), vascular disorders (57.2%), hepatobiliary disorders (38.1%) and cardiac disorders (23.7%); there were 1 (0.0%), 10 (0.3%), and 18 (0.6%) subjects experienced cardiovascular disorder, hepatic failure, and chronic kidney disease in terms of preferred term (PT). There were 1.5% and 46.8% subjects reported prior and concomitant anti-hypertensive medications, 10.2% and 94.9% subjects reported prior and concomitant anti-diabetes medication, respectively.

Exposure:

The frequency of dose for the vast majority of subjects was taken once daily with mean exposure duration of 209.1 days and no overdose was reported for all subjects.

Safety results:

At least one AE occurred in 35.4% (1059/2990) of subjects over study period, and 9.0% (268/2990) of subjects experienced an adverse drug reaction (ADR). The percentage of SAEs was 6.2% (186/2990). The incidence of AEs leading to drug permanently discontinued was 4.7%. The percentage of main AESIs was 2.3% (70/2990) for UTI, 1.3% (39/2990) for GTI, and 1.1% (32/2990) for hypoglycaemia.

Among the AEs, most of them were mild (75.35%, 798/1059) in intensity, and were not related to treatment (74.69%, 791/1059). The majority of SAEs were mild (42.47%, 79/186) and moderate (32.80%, 61/186) in intensity. For the actions taken for the SAEs, most subjects did not change their study drug doses (74.73%, 139/186) and outcome of most subjects was recovered (66.13%, 123/186). No SAEs leading to death occurred throughout the study.
For subgroup analysis of AEs, the incidence of AEs in older subjects over 65 years and subjects at 65 years and below was 40.3% and 34.5%, respectively. The percentages of subjects with overall AE in females and in males were 41.9% and 32.0%, respectively. The incidences of subjects with AE were 31.2%, 37.6%, 35.8% and 47.4% for subjects with a

duration of diabetes ≤ 5 years, >5 and ≤ 10 years, >10 and ≤ 20 years, and >20 years, respectively. Incidences of AE in subjects with impaired and normal hepatic function were 54.2% and 36.2%, and incidences of AE in subjects with mild renal impairment, moderate to severe renal impairment and normal renal function were 39.8%, 41.0% and 34.9%, respectively. The incidences of AEs for dapagliflozin in combination with at least one other anti-diabetic medication and dapagliflozin alone were 36.0% and 23.7%, respectively.

Conclusion:

The study was a 24-week multi-center, single arm, prospective cohort, observational study, which was conducted in 3000 Chinese T2DM subjects. Most subjects showed great compliance to study treatment with mean exposure duration of 209.1 days. Overall, the incidence of AEs/SAEs and AESIs, was similar to previous phase IIb/III studies, showing a favorable safety profile. This study demonstrated that once-daily dapagliflozin was well tolerated in Chinese T2DM subjects without any new safety findings. The safety profile in this study was consistent with the known safety profile of dapagliflozin as described in the current prescribing information.

Publications:

Guo Lixin, Wang Jing, Li Li, et al. The use of SGLT-2 inhibitor in clinical practice——Data from real-world study of dapagliflozin in China (DONATE); The 25th Annual Meeting of Chinese Diabetes Society (Oral Presentation), Hangzhou, China.