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PHARMACOKINETICS, SAFETY AND TOLERABILITY OF EMPAGLIFLOZIN/METFORMIN FIXED-DOSE COMBINATION VS EMPAGLIFLOZIN/METFORMIN INDIVIDUAL TABLETS IN HEALTHY SUBJECTS

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ABSTRACT

Empagliflozin is a drug of the gliflozin class, approved for the treatment of type 2 diabetes in adults in 2014. It was developed by Boehringer Ingelheim and Eli Lilly and Company. Empagliflozin is an inhibitor of the sodium glucose co-transporter-2 (SGLT-2), and causes sugar in the blood to be excreted by the kidneys and eliminated in urine. Fixed-dose combinations of Empagliflozin with metformin XR are also commercially available, providing a measure of convenience in addition to an effective mode of delivering combination therapy to improve glycemic control. Empagliflozin has been studied clinically as initial therapy in treatment-naïve patients with T2DM and as initial therapy or add-on in combination with other antidiabetic agents. Clinical trial data with Empagliflozin demonstrate clinical efficacy in terms of glycosylated hemoglobin A1C and fasting plasma glucose reductions when used both as monotherapy and as a component of two drug combination regimens for the treatment of T2DM. Extensive Phase II and Phase III clinical trial data support the use of Empagliflozin in combination with metformin. Glycemic reduction with combination is similar to the sum of the respective monotherapies, with adverse event rates similar – or more moderate – than those observed with up-titration of monotherapy or the addition of other anti-hyperglycemic agents. We aimed here to review the new implications of Empagliflozin and metformin XR fixed dose combination and discuss about the pharmacokinetics, safety, tolerability and effect of food, referring to the recently published results.

INTRODUCTION:

Type 2 diabetes is a metabolic disease by persistent hyperglycaemia resulting from progressive deficiency of insulin [1]. Hyperglycaemia is the leading risk factor associated with the enhanced risks of cardiovascular diseases and diabetes complications, such as eye disease, diabetes neuropathy, diabetes nephropathy and skin disorders [2]. Currently, health care expenditures in patients with diabetes are 2.3 times higher than in patients without diabetes [3]. Unfortunately, the incidence of type 2 diabetes increased continuously over the past three decades throughout the world, and incidence cases potentially exceed 590 million in less than a quarter of a century [4]. Therefore, glycemic control is crucial to the management of type 2 diabetes and prevention of diabetes complications [5]. It has been well established that the improved glycemic control contributes to the reduction of cardiovascular events and amelioration of

the metabolic abnormalities in patients with diabetes [6]. In general, metformin is the most commonly used drug for patients with type 2 diabetes benefiting from its efficacy, safety, weight neutrality, low cost and potential cardiovascular benefits [1,7]. However, several patients are unable to achieve glycemic targets using metformin alone with progressive deterioration of β-cell function. Combination therapy (dual or triple) with different mechanism of anti-diabetic agents is inevitably initiated for the management of type 2 diabetes. The drugs selection in combination therapy must balance therapeutic efficacy, safety, costs, drug-drug interactions and patients' adherence. Empagliflozin is a good candidate as an add-on therapy to metformin based on its different glucose-lowering mechanism that improves glycemic control through inhibiting SGLT2-mediated renal glucose reabsorption [8]. Empagliflozin shows good pharmacokinetic behaviors, including high bioavailability and negligible risk of drug-drug interactions. Moreover, it can reduce tissue glucose disposal and increase endogenous glucose production. Metformin increases the glucose-lowering efficacy of empagliflozin through inhibiting endogenous glucose production, which potentially results in the long-term improvement of glycemic control.

Empagliflozin/metformin fixed-dose tablet combining two different glucose-lowering mechanisms is available in the USA and Europe as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes [9]. Compared with metformin monotherapy, combination therapy with empagliflozin and metformin provided synergetic glucose-lowering activity in patients with type 2 diabetes [10]. In addition, fixed-dose tablet could simplify the dosing/timing schedule, improve patient's adherence, and offers potential cost advantages. In the United States, empagliflozin/metformin hydrochloride fixed-dose tablet is available in four different dosages approved for twice-daily use: 5/500 mg, 5/1000 mg, 12.5/500 mg, and 12.5/1000 mg [9]. We searched the MEDLINE and PubMed databases with the titles "empagliflozin" and "metformin" to identify all clinical trials evaluating empagliflozin/metformin combination therapy in patients with type 2 diabetes, together with the abstracts and posters of the annual meetings of the American Diabetes Association and the European Association for the Study of Diabetes 2012-2017. ClinicalTrials.gov. was also searched to identify unpublished trials.

Empagliflozin and metformin have complementary mechanisms of action [9]. Empagliflozin inhibits SGLT2, the predominant transporter responsible for a significant proportion of glucose reabsorption from the glomerular filtrate back into the systemic circulation, and increases urinary glucose excretion, which reduces hyperglycaemia in patients with type 2 diabetes [9,11]. Metformin lowers hepatic glucose production through stimulating AMP-activated protein kinase [12]. In addition, metformin can increase insulin sensitivity, enhance peripheral glucose uptake and reduce the absorption of glucose from the gastrointestinal tract (GIT) [13].

Empagliflozin has potency and high selectivity in inhibiting SGLT 2 [14]. In vitro studies showed that the half-maximal inhibition concentration (IC50) of empagliflozin was 3.1 nmol/L for SGLT2, but was less potent for other SGLTs (IC50 range: 1100-11000 nmol/L) [14]. Empagliflozin shows > 2,500-fold selectivity for inhibition of SGLT2 versus SGLT1 [14]. Empagliflozin can inhibit the reabsorption of glucose in individuals with or without type 2 diabetes [15]. Patients with type 2 diabetes were randomly assigned to receive different doses empagliflozin 10, 25 or 100 mg once-daily, and the corresponding inhibition of renal tubular glucose reabsorption rate were 36%, 42% and 45% on day 1, respectively [16]. Inhibition of glucose reabsorption was maintained at 36-48% following multiple doses of empagliflozin once-daily (day 27) [16]. Reductions from baseline in fasting plasma glucose (FPG) were observed in all dose groups. Mean FPG reduced from 10.33 mmol/L on the first day to 8.17 mmol/L on the 28th day in patients treated with 10 mg

empagliflozin, from 9.28 mmol/L to 7.39 mmol/L with 25 mg, and from 8.33 mmol/L to 6.67 mmol/L with 100 mg, compared with 8.56 mmol/L to 8.33 mmol/L with placebo [16]. Several clinical trials are being performed or designed to investigate the efficacy and safety of empagliflozin in patients with type 1 diabetes as adjunctive therapy to insulin [17,18,19]. In a single-arm open-label proof-of-concept trial, patients recruited were treated with 25 mg oral once daily. Mean Hemoglobin A1c (HbA1c) decreased from 8.0 ± 0.9% to 7.6 ± 0.9% (P < 0.0001), and mean FPG fell from 9.0 ± 4.3 to 7.0 ± 3.2 mmol/L (P = 0.008). Total daily insulin decreased benefiting from the reduced basal insulin (25.7 ± 10.6 to 19.5 ± 7.9 units, P < 0.0001). Urinary glucose excretion (UGE) increased significantly from 177 ± 121 to 229 ± 160 g/24 h (P = 0.0007) [20].

Metformin is extensively recommended as a first-line therapy in patients with type 2 diabetes benefiting from its good efficacy, low risk of hypoglycaemia, and weight neutrality [21]. Its glucose-lowering effect mainly involves inhibition of hepatic gluconeogenesis, reduction of insulin resistance and enhancement of peripheral insulin sensitivity [22]. In addition, metformin potentially reduces fatty acid oxidation and improves functional activity of glucose transporters, as well as insulin-mediated insulin receptor tyrosine kinase activity [23].

2.0 Participants and methods

`Healthy male and female (non-pregnant and non-lactating) subjects who were agde 18 to 55 years, body mass index (BMI) 18.5 to 29.9 kg/m2 considered healthy based on medical history, physical examination and clinical laboratory evaluations were eligible to partcipate in the study. We considered, all the protocols of the studies were approved by Ethics committee at their respective site and studies were conducted in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the protocol. All subjects were given written informed consent before participation of the study.

3.0 Study design:

`The objective of this trial was to investigate the relative bioavailability (BA) of two FDC extended release (XR) tablets (25 mg/1000 mg [Test1, T1] and 2 x 12.5 mg/750 mg [T2] Empagliflozin/ Metformin) vs. the free combination of 25 mg Empagliflozin [Reference 1, R1] and 500 mg Metformin (Glumetza®) [R2], XR tablets.
This is a randomised, open-label, 3-weeks duration, two-way crossover design in each of the three individual study parts:

Part a: 25 mg Empagliflozin/1000 mg Metformin XR FDC versus the single tablets under fasted conditions (Treatment A [FDC1000Fast] and B [E+M1000Fast])

Part b: 25 mg Empagliflozin/1000 mg Metformin XR FDC versus the single tablets under fed conditions (Treatment C [FDC1000Fed] and D [E+M1000Fed])

Part c: 2 x 12.5 mg Empagliflozin/750 mg Metformin XR FDC (25 mg/1500 mg) versus the single tablets under fasted conditions (Treatment E [FDC1500Fast] and F [E+M1500Fast]).
Treatments administered:
No. of Subjects:
Planned: Entered: 72 (24 in each trial part)
Actual: Entered: 72 Completed: 71

4.0 Evaluation Criteria:

Clinical Pharmacology:

Primary endpoints: AUC0-tz and Cmax for both Empagliflozin and Metformin
Secondary endpoint: AUC0-∞ for both Empagliflozin and Metformin

Safety: Adverse events (AEs), safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure, pulse rate), and physical examination.

Statistical Methods:

Relative bioavailability was estimated by the ratios of the geometric means (Test/Reference) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) were provided for information purpose only. The statistical model was an analysis of variance (ANOVA) on the logarithmic scale including effects for 'sequence', 'subjects within sequences', 'period' and 'treatment'. Confidence intervals were calculated based on the residual error from ANOVA. Descriptive statistics were calculated for all endpoints. No interim analyses were conducted.

5.0 RESULTS AND DISCUSSION:

`Of the 72 healthy volunteers entered, 71 (41 males and 30 females) completed all treatments as planned while 01 subject discontinued the trial due to non-compliance with the protocol. Consequently, 23 subjects received Treatment A and B (25 mg Empagliflozin/1000 mg Metformin FDC vs. the single tablets under fasted conditions), 24 subjects received Treatment C and D (25 mg Empagliflozin/1000 mg Metformin FDC vs. the single tablets under fed conditions), and 24 subjects received Treatment E and F (2 x 12.5 mg Empagliflozin/750 mg Metformin FDC vs. the single tablets under fasted conditions). Forty-one subjects were White, 29 were Black or African American, and 1 was Asian with a mean (SD) age of 32.5 (8.8) years and BMI of 25.76 (3.07) kg/m2.

Clinical pharmacology:

`For each study part, geometric mean (gMean) plasma concentration- time profiles and pharmacokinetic parameters of Empagliflozin and Metformin were similar for the FDC and the free dose combination. The adjusted gMean ratios (FDC to free dose combination), 2-sided 90% CIs, and intra-subject geometric coefficient of variation (gCV) values for all primary and secondary endpoints are summarised in the following table.

Safety:

`After 71 subjects were treated with Empagliflozin and Metformin, 14 (19.7%) reported AEs. Two out of 23 subjects (8.7%) reported AEs after treatment with E+M1000Fast, 05/23 (21.7%) after FDC1000Fast, 02/24 (8.3%) each after E+M1000Fed and FDC1000Fed, respectively, 01/24 (4.2%) after E+M1500Fast, and 04/24 (16.7%) after FDC1500Fast. The most frequent AE was headache and occurred to 06 subjects (03 subjects after FDC1000Fast, 01 after E+M1000Fed, and 02 after FDC1500Fast). The second most frequent AE was nausea, reported for 05 subjects (01 subject after E+M1000Fast, 02 after FDC1000Fast, 02 after E+M1000Fed, 01 after FDC1000Fed, and 01 after E+M1500Fast). Abdominal pain and diarrhoea were reported in 03 subjects each and vomiting occurred in 02 subjects. The majority of the AEs were of mild intensity; only 03 AEs (nausea and vomiting) were of moderate intensity. No AE of severe intensity occurred. All AEs were considered drug-related by the investigator. Therapy was required for 01 mild AE and all subjects recovered. No AEs led to premature discontinuation of the trial. No deaths, no serious AEs or clinically relevant findings in laboratory evaluation, physical examination, vital signs, or 12-lead ECG were reported.

6.0 CONCLUSION:

`The relative bioavailabilities of Empagliflozin and Metformin XR FDC tablets versus the free dose combination of Empagliflozin and Metformin XR tablets were investigated for 2 FDC tablet strengths (25 mg/1000 mg and 12.5 mg/750 mg) under fasted (both tablet strengths) and fed (25 mg/1000 mg) conditions. All adjusted gMean ratios FDC to free dose combination for AUC0-tz and Cmax of Empagliflozin and Metformin were within the bioequivalence limits of 80.00 to 125.00%. Furthermore, administration of the FDC tablet was well tolerated in healthy subjects.

Treatment	Product
Treatment A	25 mg Empagliflozin/1000 mg Metformin XR FDC (T1 fasted).
	Entered: 24; Treated: 23; Analysed (for primary endpoint): 23.
Treatment B	25 mg Empagliflozin/1000 mg Metformin XR (R1 fasted).
	Entered: 24; Treated: 23; Analysed (for primary endpoint): 23.
Treatment C	25 mg Empagliflozin/1000 mg Metformin XR FDC (T1 fed).
	Entered: 24; Treated: 24; Analysed (for primary endpoint): 24.
Treatment D	25 mg Empagliflozin/1000 mg Metformin XR (R1 fed).
	Entered: 24; Treated: 24; Analysed (for primary endpoint): 24.
Treatment E	2 x 12.5 mg Empagliflozin/750 mg Metformin XR FDC (T2 fasted).
	Entered: 24; Treated: 24; Analysed (for primary endpoint): 24.
Treatment F	2 x 12.5 mg Empagliflozin/750 mg Metformin XR (R2 fasted).
	Entered: 24; Treated: 24; Analysed (for primary endpoint): 24.

Treatments administered:

The treatments administered in this study were as follows

	Investigational (Test)	**Comparator (Reference)**
Products		
Part a, Part b & Part c	25 mg Empagliflozin/1000 mg Metformin XR FDC tablet; 12.5 mg Empagliflozin/750 mg Metformin XR FDC tablet	Empagliflozin 25 mg tablet, Glumetza® 500 mg tablet
Dose		
Part a	1 x 25 mg Empagliflozin/1000 mg Metformin XR, fasted (Treatment A)	1 x 25 mg Empagliflozin + 2 x 500 mg Metformin XR (Glumetza®), fasted (Treatment B)
Part b	1 x 25 mg Empagliflozin/1000 mg Metformin XR, fed (Treatment C)	1 x 25 mg Empagliflozin + 2 x 500 mg Metformin XR (Glumetza®), fed (Treatment D)
Part c	2 x 12.5 mg Empagliflozin/750 mg Metformin XR, fasted (Treatment E)	1 x 25 mg Empagliflozin + 3 x 500 mg Metformin XR (Glumetza®), fasted (Treatment F)

Analysis of relative bioavailability of Empagliflozin and Metformin after administration of Empagliflozin and Metformin XR as FDC or free dose combination

Analyte Parameter	Adjusted gMean FDC	Adjusted gMean free dose combination	Adjusted gMean ratio FDC/free dose combination [%]	90% CI upper limit, lower limit [%]	Intra-individual gCV [%]
Study part a: 25 mg Empagliflozin/1000 mg Metformin XR fasted					
Empagliflozin (FDC, N=23, free dose combination N=23)					
AUC0-tz [nmol·h/L]	6434.8	6436.4	99.98	97.3, 102.8	5.4
Cmax [nmol/L]	886.1	812.4	109.07	99.9, 119.1	17.4
AUC0-∞ [nmol·h/L]	6508.7	6502.0	100.10	97.6, 102.7	5.1

Analyte Parameter	Adjusted gMean FDC	Adjusted gMean free dose combination	Adjusted gMean ratio FDC/free dose combination [%]	90% CI upper limit, lower limit [%]	Intra-individual gCV [%]
Metformin (FDC, N=23, free dose combination N=23)					
AUC0-tz [nmol·h/L]	6351.6	6710.5	94.65	82.3, 108.9	28.1
Cmax [nmol/L]	822.3	850.8	96.65	83.3, 112.1	29.8
AUC0-∞ [nmol·h/L]	6493.4	6806.1	95.40	82.4, 110.4	29.4
Study part b: 25 mg Empagliflozin/1000 mg Metformin XR fed					
Empagliflozin (FDC, N=24, free dose combination N=24)					
AUC0-tz [nmol·h/L]	5679.7	5849.9	97.09	93.9, 100.4	6.7
Cmax [nmol/L]	555.8	601.4	92.42	86.8, 98.4	12.5
AUC0-∞ [nmol·h/L]	5790.3	5968.5	97.01	93.6, 100.5	7.0
Metformin (FDC, N=24, free dose combination N=24)					
AUC0-tz [nmol·h/L]	13040.2	13080.2	99.69	96.3, 103.3	7.1
Cmax [nmol/L]	1181.5	1072.4	110.17	103.8, 116.9	12.0
AUC0-∞ [nmol·h/L]	13194.2	13243.2	99.63	96.2, 103.2	7.1
Study part c: 2 x 12.5 mg Empagliflozin/750 mg Metformin XR fasted					
Empagliflozin (FDC, N=24, free dose combination N=24)					
AUC0-tz [nmol·h/L]	7159.3	7109.3	100.70	98.3, 103.2	4.9
Cmax [nmol/L]	1014.8	963.1	105.37		96.6, 114.9
AUC0-∞ [nmol·h/L]	7237.3	7181.0	100.78	98.4, 103.3	4.9
Metformin (FDC, N=24, free dose combination N=24)					
AUC0-tz [nmol·h/L]	10229.0	10253.2	99.76	88.7, 112.3	24.2
Cmax [nmol/L]	1300.8	1331.8	97.68	86.9, 109.7	23.8
AUC0-∞ [nmol·h/L]	10540.8	10430.1	101.06	89.7, 113.9	24.4

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