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Research Article

PHARMACOKINETICS, SAFETY AND FOOD EFFECT OF SINGLE DOSE LINAGLIPTIN/METFORMIN XR FIXED DOSE COMBINATION (FDC) VS LINAGLIPTIN AND METFORMIN XR FREE COMBINATION IN HEALTHY ADULT SUBJECTS

Laxmi V. Ponnam *

Sr. Resident, District Govt hospital, Sangareddy, Telangana, INDIA.

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ABSTRACT

Linagliptin is a selective dipeptidyl peptidase-4 inhibitor recently marketed for once-daily administration in the treatment of type 2 diabetes mellitus (T2DM). Fixed-dose combinations of Linagliptin 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. Linagliptin 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 Linagliptin 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 Linagliptin 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 antihyperglycemic agents. We aimed here to review the new implications of Linagliptin and metformin XR fixed dose combination and discuss about the pharmacokinetics, safety, tolerability and effect of food, referring to the recently published results.

KEYWORDS: *Pharmacokinetics, Linagliptin, Metformin, FDC.*

INTRODUCTION

Type 2 diabetes and the associated cardiovascular morbidity pose globally one of the most serious public health threats of the 21st century. Despite the availability of a great variety of antidiabetic agents (oral and injectable), a large number of diabetic patients remain inadequately controlled [1]. The difficulty to achieve and sustain glycemic control over time is mainly related to the inevitably progressive nature of the disease, the increased risk of treatment-related adverse effects (such as hypoglycemia and weight gain), and the poor adherence of patients to treatment due to complex therapeutic regimens [1, 2]. To overcome these challenges, antidiabetic regimens with safety, efficacy, convenience, and flexibility are urgently required.

Combination therapies with two antidiabetic agents are a widely accepted approach to type 2 diabetes treatment, resulting from the common failure of monotherapy to achieve sufficient metabolic control [1]. The agents that are combined should ideally display complementary mechanisms of action and have compatible pharmacokinetic characteristics. In the author's opinion, the combination of these agents into a single tablet may offer a better therapeutic option, since it considerably simplifies the therapeutic regimen, possibly also maximizing patients' compliance and often resulting in a lower cost of treatment.

In such fixed-dose combinations, the one compound is usually metformin, which has traditionally been used as first-line treatment in type 2 diabetes for more than 30 years. A promising candidate for co-administration with metformin are gliptins or dipeptidyl peptidase-4 (DPP-4) inhibitors, a relatively novel, incretin-based, antidiabetic drug category with well-documented antihyperglycemic efficacy and an excellent tolerability profile [3]. Clinical trials have shown that combining metformin with DPP-4 inhibitors produces better glycemic control in inadequately controlled type 2 diabetic patients, compared to individual monotherapy [4, 5].

Among all available gliptins, linagliptin has some unique characteristics such as favorable pharmacokinetic properties, simple dosing regimen, high potency, and selectivity for DPP-4 inhibition [6–9]. Recently, a fixed-dose, singletablet, combined formulation of metformin and linagliptin was approved for use in type 2 diabetic patients as an adjunct to diet and exercise, either alone or combined with sulfonylureas. Approval was gained in May 27, 2016in the United States [10]. Clinical evidence suggests that this combination significantly improves key parameters of glucose metabolism and has an optimal safety profile [11]. The pharmacodynamic effects of linagliptin complement the suppression of hepatic glucose production and improved insulin sensitivity accomplished with metformin, while its pharmacokinetic parameters are totally compatible with those of metformin. This indicates that linagliptin/metformin fixed-dose combination can adequately address multiple abnormalities of type 2 diabetes pathophysiology, and emerges, thus, as an attractive alternative option for the treatment of type 2 diabetes.

Metformin decreases elevated blood glucose with predominant effects on fasting hyperglycaemia by reducing hepatic glucose output and increasing insulin sensitivity [12]. In addition, obese non-diabetic subjects treated with metformin have been shown to have a 1.5- to 2-fold increase in active GLP-1 concentrations following an oral glucose load [13, 14]. This effect of metformin on GLP-1 levels was not due to DPP-4 inhibition. Therefore, combination therapy with metformin and DPP-4 inhibitors may be expected to effectively lower glucose because of their different mechanisms of action as initial combination therapy with metformin [15]. Metformin immediate-release (IR) formulations given twice daily are usually considered therapeutically interchangeable with the same daily dose of metformin extended-release (XR) formulations given at doses up to 2 g once daily with the evening meal [12].

***Corresponding author:**

Dr. Laxmi V. Ponnam

Sr. Resident,

District Govt hospital, Sangareddy,

Telangana, INDIA.

E-Mail: drlaxmiponnam@gmail.com

The use of fixed-dose combination (FDC) formulations of two or more therapeutic agents with complementary mechanisms of action has been increasing in the clinical setting. With the goal of optimizing patient compliance, Linagliptin/metformin XR FDCs have been developed in order to improve ease of administration as compared with taking two individual component tablets and to allow the convenience of once-daily dosing compared with twice-daily IR metformin formulations. The linagliptin/metformin XR FDC formulations employ the same manufacturing technology as used in the single-component linagliptin formulation. The objectives of the studies described here were to establish bioequivalence for linagliptin and metformin administered as Linagliptin/metformin XR FDC tablets and administered in corresponding doses as individual tablets, thereby bridging the clinical safety and efficacy data generated by phase III studies of co-administration of individual linagliptin and metformin tablets to the linagliptin/metformin XR FDC tablets. Additionally, the steady-state pharmacokinetic profile of the highest strength linagliptin/metformin XR 5 mg/1000 mg FDC tablet was examined to ensure consistency of performance and absence of dose-dumping of metformin from the formulation.This review analyzes the rationale for combining linagliptin and metformin XR into a single tablet in a fixed-dose combination, and provides an overview of clinical, pharmacodynamics, and pharmacokinetic data supporting its use in type 2 diabetes treatment.

MATERIALS 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.

Study Design:

The objective was to establish the bioequivalence of linagliptin/metformin extended release (XR) fixed dose combination (FDC) tablets versus the free combination of linagliptin tablets and metformin XR tablets under fasted (Part 1) and fed (Part 2) conditions.
This was a randomised, open-label, single-dose, 2-way crossover trial with 2 individual study parts:

Part 1: one 5 mg linagliptin/1000 mg metformin XR FDC tablet versus the free combination (1 tablet 5 mg linagliptin and 2 tablets 500 mg Metformin XR) under fasted conditions

Part 2: one 5 mg linagliptin/1000 mg metformin XR FDC tablet versus the free combination (1 tablet 5 mg linagliptin and 2 tablets 500 mg metformin XR) under fed conditions.

A total of 68 subjects were planned to include in the study. Out of 68 subjects, 52 subjects will receive the treatments in fasted conditions and 16 subjects in fed conditions.

Part 1 (fasted conditions): A total of 52 subjects were treated with FDC product and from that all 52 subjects were analysed and 52 subjects were free combination and from that all 52 subjects were analysed.

Part 2 (fed conditions): A total of 14 subjects were treated with FDC product and from that all 14 subjects were analysed and 15 subjects were free combination and from that all 15 subjects were analysed.

Treatments administered:

This is an open label, randomized, crossover study to evaluate the clinical pharmacololgy and safety of Linagliptin 5 mg & metformin 1000 mg XR when administered as FDC or free combinations.

Part 1 (n=52; fasted conditions):

Investigational product: Linagliptin 5 mg/metformin 1000 mg XR FDC tablet.

Comparator product: Linagliptin 5 mg (1 tablet of Tradjenta® 5 mg) and metformin XR 1000 mg (2 tablets of Glumetza® 500 mg).

A single dose or either of the treatments were administered vial oral route with 240 mL of water after an overnight fast of at least 10 h for the fasted study part in each period.

Part 2 (n=16; fed conditions):

Investigational product: Linagliptin 5 mg/metformin 1000 mg XR FDC tablet.

Comparator product: Linagliptin 5 mg (1 tablet of Tradjenta® 5 mg) and metformin XR 1000 mg (2 tablets of Glumetza® 500 mg)
A single dose of either of the treatments were administered vial oral route with 240 mL of water after a high-fat, high-calorie meal for the fed study part in each period.

Evaluation criteria:

Pharmacokinetics: The following pharmacokinetic parameters were evaluated as primary endpoints: AUC0-72 and Cmax for linagliptin, AUC0-tz and Cmax for metformin The following pharmacokinetic arameters were evaluated as secondary endpoints: AUC0-∞ for both linagliptin and metformin.

Safety: The evaluation of safety was based on: adverse events (including clinically relevant findings from the physical examination), safety laboratory tests, vital signs (blood pressure, pulse rate), 12-lead electrocardiogram (ECG).

Statistical methods: The assessment of bioequivalence was based upon 2-sided 90% confidence intervals (CIs) for the ratios of the geometric means (FDC/free combination) for the primary endpoints using an acceptance range of 80.00 to 125.00%. This method is equivalent to the two 1-sided t-tests procedure, each at the 5% significance level. The statistical model was an analysis of variance (ANOVA) on the logarithmic scale including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. CIs were calculated based on the residual error from ANOVA. Descriptive statistics were calculated for all endpoints. No interim analysis was performed.

RESULTS

A total of 68 healthy volunteers participated in the study. Fifty-two subjects participated in Part 1, all of whom completed the study as planned. Twenty-three study participants were male (44.2%) and 29 were female (55.8%). Age ranged from 19 to 54 years (mean: 34.7 years, standard deviation [SD]: 10.4 years), and BMI ranged from 19.1 to 29.1 kg/m2 (mean: 23.93 kg/m2, SD: 2.47 kg/m2).

Sixteen subjects participated in Part 2, three of whom prematurely discontinued study participation. Two subjects discontinued due to adverse events: 1 subject after having been treated with the free combination and 1 subject after having been treated with the FDC in the first treatment period. One subject withdrew consent after having been treated with the free combination. Six study participants were male (37.5%) and 10 were female (62.5%). Age ranged from 18 to 53 years (mean: 36.1 years, SD: 11.9 years), and BMI ranged from 19.6 to 29.1 kg/m2 (mean: 24.54 kg/m2, SD: 2.96 kg/m2).

All 68 subjects in this study were White. No relevant medical history or baseline conditions were reported for any of the participating subjects. All subjects were treated with at least 1 dose of study medication. No important protocol violations were reported.

Pharmacokinetic results:

Geometric mean (gMean) plasma concentration-time profiles and pharmacokinetic parameters of linagliptin and metformin were similar for the FDC and the free combination in each study part. The adjusted gMean values, the adjusted gMean ratios (FDC to free combination), 2-sided 90% CIs, and intra-subject geometric coefficient of variation (gCV) values for all primary and secondary endpoints are summarised in Table 1 below.

For each study part, the adjusted gMean ratios FDC to free combination for the primary endpoints (AUC0-72 and Cmax of linagliptin and AUC0-tz and Cmax of metformin) were close to 100%,

with their corresponding 90% CIs within the pre-defined acceptance range for bioequivalence of 80.00 to 125.00%. The adjusted gMean ratios for the secondary endpoint, AUC0-∞ of linagliptin and metformin, were close to 100%, with their corresponding 90% CIs within the acceptance range for bioequivalence, except for AUC0-∞ of linagliptin under fed conditions, for which the lower limit of the 90% CI was outside the bioequivalence limit.

Table No. 1: Analysis of bioequivalence of Linagliptin and Metformin after administration of 5 mg Linagliptin and 1000 mg Metformin XR as FDC or free combination

Analyte Parameter	Adjusted gMean FDC	Adjusted gMean free combination	Adjusted gMean ratio FDC/free combination [%]	90% CI (upper limit, lower limit) [%]	Intra individual gCV [%]
Part 1 (fasted conditions)					
Linagliptin (FDC N=52, free combination N=52)					
AUC0-72 [nmol·h/L]	288	287	100.4	(96.6, 104.3)	11.8
Cmax [nmol/L]	9.54	8.83	108.1	(99.0, 118.0)	27.1
AUC0-∞ [nmol·h/L]	460	461	99.7	(95.2, 104.5)	14.3
Metformin (FDC N=52, free combination N=52)					
AUC0-tz [ng·h/mL]	7146	7147	100	(93.0, 107.5)	22.2
Cmax [ng/mL]	924	926	99.8	(92.5, 107.6)	23.4
AUC0-∞ [ng·h/mL]	7540	7608	99.1	(92.4, 106.4)	21.7
Part 2 (fed conditions)					
Linagliptin (FDC N=14, free combination N=15)					
AUC0-72 [nmol·h/L]	222	234	94.7	(88.7, 101.1)	9.2
Cmax [nmol/L]	5.69	5.79	98.2	(94.1, 102.6)	6.1
AUC0-∞ [nmol·h/L]	387	398	97.4	(77.1, 123.0)	32.4
Metformin (FDC N=14, free combination N=15)1					
AUC0-tz [ng·h/mL]	10980	11326	97	(92.2, 101.9)	7.1
Cmax [ng/mL]	938	947	99	(95.0, 103.2)	5.9
AUC0-∞ [ng·h/mL]1	14774	15047	98.2	(93.3, 103.3)	7.2

1 One subject excluded from AUC0-∞ calculation for the FDC (FDC N=13, free combination N=15)

Safety and tolerability Results:

Single oral doses of linagliptin 5 mg and metformin XR 1000 mg as the FDC tablets or as free combinations were generally well tolerated by healthy adult subjects in both parts.

During the treatment periods of the 2 study parts, adverse events (AEs) were reported for a total of 26 subjects (38.2%). No deaths, protocol-specified adverse events of special interest (AESIs), or other significant AEs according to ICH E3 were reported in this study. All AEs had either resolved by the end of the study or had been sufficiently followed-up. There were no clinically relevant findings with respect to safety laboratory tests, vital signs, or ECG.

In Part 1, AEs were reported for 10 of 52 subjects (19.2%) during the treatment period with the free combination and for 13 of 52 subjects (25.0%) during the treatment period with the FDC tablet. All AEs were of mild or moderate intensity; no serious adverse events (SAEs) were reported in this study part. Four subjects (7.7%) reported AEs that were assessed as drugrelated by the investigator (headache and diarrhoea). AEs reported for more than 1 subject in this study part at the preferred term level were headache (7 subjects, 13.5%), diarrhoea (4 subjects, 7.7%), dizziness, rhinitis, nasopharyngitis, and back pain (reported for 2 subjects each, 3.8%).

In Part 2, AEs were reported for 5 of 15 subjects (33.3%) during the treatment period with the free combination and for 4 of 14 subjects (28.6%) during the treatment period with the FDC tablet. Two subjects were reported with SAEs after treatment with the free combination: 1 subject had a fall and 1 subject had a road traffic accident, 26 and 15 days after the day of drug intake, respectively. The SAEs were severe in intensity; all other AEs were of mild or moderate intensity. One subject terminated the study prematurely after treatment with the FDC due to a suspected drug-induced allergic skin reaction (rash). Five subjects (31.3%) reported AEs that were assessed as drug-related by the investigator (headache, decreased appetite, vertigo, diarrhoea, abdominal discomfort, and rash). The most frequently reported AE (reported for more than 1 subject) in this study part at the preferred term level was headache (2 subjects, 12.5%).

DISCUSSION

Linagliptin 5mg and metformin 1000 mg XR were administered and pharmacokinetic, safety and tolerability were evaluated in healthy subjects in this study. The bioequivalence studies conducted in healthy subjects in this study parts with linagliptin 5 mg and metformin 1000 mg XR had no clinically meaningful drug interaction between the pharmacokinetics of either drug. This is suggesting that the two drugs could be combined into a single FDC tablet. The present studies evaluated the bioequivalence of Linagliptin 5 mg/metformin 1000 mg XR FDC tablet compared to free combination of Linagliptin 5 mg and metformin 1000 mg XR tablets.

Linagliptin 5 mg and metformin 1000 mg XR showed in each study part, the adjusted gMean ratios FDC to free combination for the primary endpoints (AUC0-72 and Cmax of linagliptin and AUC0-tz and Cmax of metformin) were close to 100%, with their corresponding 90% CIs within the pre-defined acceptance range for bioequivalence of 80.00 to 125.00%. The adjusted gMean ratios for the secondary endpoint, AUC0-∞ of linagliptin and metformin, were close to 100%, with their corresponding 90% CIs within the acceptance range for bioequivalence, except for AUC0-∞ of linagliptin under fed conditions, for which the lower limit of the 90% CI was outside the bioequivalence limit.

The safety findings observed in this study were consistent with those previously reported for individual tablets of linagliptin 5 mg and metformin 1000 mg XR in healthy subjects. Findings from both parts of the study in healthy subjects demonstrated favourable safety and tolerability of linagliptin when administered concomitantly with metformin XR tablets.

CONCLUSIONS

The fixed-dose combination tablet of 5 mg linagliptin/1000 mg metformin XR was bioequivalent to single tablets 5 mg linagliptin and 1000 mg metformin XR administered together, both under fasted and fed conditions. All adjusted geometric mean ratios FDC/free combination for AUC0-72 and Cmax of linagliptin, and AUC0-tz and Cmax of metformin were close to 100% with their corresponding 90% CIs within the pre-defined acceptance range of 80.00 to 125.00%. All treatments investigated in this study were safe and well tolerated in healthy male and female subjects.

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