ALOGLIPTIN/METFORMIN HCL IMMEDIATE RELEASE TABLETS
FIXED- DOSE COMBINATION: SINGLE DOSE SAFETY, TOLERABILITY
AND FOOD EFFECT IN HEALTHY VOLUNTEERS
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ABSTRACT
Alogliptin 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 alogliptin with metformin are also commercially available, providing a measure of convenience in addition to an effective mode of delivering combination therapy to improve glycemic control. Alogliptin 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 alogliptin 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 alogliptin 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 alogliptin and metformin fixed dose combination (AMFDC) and discuss about the pharmacokinetics, safety, tolerability and effect of food, referring to the recently published papers.

Key Words: antidiabetic, diabetes management, DPP-4 inhibitor, fixed-dose combination, incretin therapy.

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INTRODUCTION
Alogliptin is a potent, highly selective (1), orally available inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme. DPP-4 is thought to be primarily responsible for the in vivo degradation of two incretin hormones released in response to nutrient ingestion (2), namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin tropic peptide (GIP). Both peptide hormones exert important effects on islet beta cells to stimulate glucose-dependent insulin secretion as well as to stimulate proliferation and inhibit apoptosis of beta cell (3–5). GLP-1 also suppresses glucagon secretion from pancreatic alpha cells, delays gastric emptying and reduces food intake (4,6). The glucose-lowering actions of GLP-1, but not GIP, are relatively well preserved in patients with type 2 diabetes mellitus (2, 5, 7). Metformin is the most commonly prescribed first-line drug worldwide for the treatment of type 2 diabetes; it acts by decreasing both hepatic
glucose production and intestinal glucose absorption, while improving insulin sensitivity (8). Metformin monotherapy may, however, fail to maintain glucose control over time, largely because of the progressive loss of beta-cell function in patients with type 2 diabetes (9,10). While other classes of antihyperglycaemic agents have been used successfully in combination with metformin when metformin alone fails to maintain glycaemic control, side effects of weight gain and hypoglycaemia are commonly observed (11,12).

In response to the globally rising incidence and burden of type 2 diabetes (13) and to the limitations of the currently available treatments for glycaemic control, DPP-4 inhibitors have emerged as a new class of antihyperglycaemic agents for use as monotherapy and add-on therapy with other agents, including metformin. Inhibition of DPP-4 with sitagliptin and vildagliptin has been shown to improve glycaemic control in patients with type 2 diabetes by inhibiting the degradation of GLP-1 and GIP (11,14,15). Given their complementary mechanisms of action, the addition of DPP-4 inhibitors, such as alogliptin, to ongoing metformin therapy may provide synergistic glycaemic control. The aim of this study was to evaluate the efficacy and safety over 26 weeks of alogliptin at once-daily doses of 12.5 and 25 mg compared with placebo in combination with metformin in patients whose HbA1c levels were inadequately controlled on metformin alone.

PARTICIPANTS AND METHODS
Healthy men or non-pregnant, non-lactating women and an overall age ranging from 18 to 55 who were considered healthy based on medical history, physical examination and clinical laboratory evaluations were enrolled in these studies. Overall of the participated subjects ranging from 18 to 32 and with more than 50 kg of weight were enrolled 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

All of the five studies were randomized, open-label, single center, crossover trials consisting of healthy subjects hospitalized for at least 05 days in each period and a minimum washout period of 07 days was maintained. (Takeda Clinical trial Protocol Numbers are: Study I: SYR-322MET_101; Study II: SYR-322MET_103; Study III: SYR-322-MET/CPH-001; Study IV: SYR-322MET_102 and Study V: SYR-322-MET/CPH-002).

Study I was an Open-Label, Randomized, 2-Cohort, 4-Sequence, 4-Period Crossover Study to Determine the Bioequivalence of Alogliptin 6.25 mg and 12.5 mg and Metformin 500 mg and 1000 mg When Administered as Individual Tablets and as a Fixed-Dose Combination Tablet. In this study healthy subjects received either of the following treatments,
Cohort 1 (n=48):
- Treatment A: Alogliptin 6.25 mg + Metformin 500 mg FDC tablet (Test)
- Treatment B: Alogliptin 6.25 mg and Metformin 500 mg individual tablets (Reference)
- Treatment C: Alogliptin 6.25 mg + Metformin 1000 mg FDC tablet (Test)
- Treatment D: Alogliptin 6.25 mg and Metformin 1000 mg individual tablets (Reference)

Cohort 1 (n=48):
- Treatment E: Alogliptin 12.5 mg + Metformin 500 mg FDC tablet (Test)
- Treatment F: Alogliptin 12.5 mg and Metformin 500 mg individual tablets (Reference)
- Treatment G: Alogliptin 12.5 mg + Metformin 1000 mg FDC tablet (Test)
- Treatment H: Alogliptin 12.5 mg and Metformin 1000 mg individual tablets (Reference)

Study II was an Open-Label, Randomized, 2-Cohort, 4-Sequence, 4-Period Crossover Study to Determine the Bioequivalence of Alogliptin 6.25 mg and 12.5 mg and Glucophage (metformin HCl) 500 mg and 1000 mg When Administered as Individual Tablets and as a Fixed-Dose Combination Tablet. In this study healthy subjects received either of the following treatments,

Cohort 1 (n=36):
- Treatment A: Alogliptin 6.25 mg + Metformin 500 mg FDC tablet (Test)
- Treatment B: Alogliptin 6.25 mg and Metformin 500 mg individual tablets (Reference)
- Treatment C: Alogliptin 6.25 mg + Metformin 1000 mg FDC tablet (Test)
- Treatment D: Alogliptin 6.25 mg and Metformin 1000 mg individual tablets (Reference)

Cohort 1 (n=36):
- Treatment E: Alogliptin 12.5 mg + Metformin 500 mg FDC tablet (Test)
- Treatment F: Alogliptin 12.5 mg and Metformin 500 mg individual tablets (Reference)
- Treatment G: Alogliptin 12.5 mg + Metformin 1000 mg FDC tablet (Test)
- Treatment H: Alogliptin 12.5 mg and Metformin 1000 mg individual tablets (Reference)

Study III was A Randomized, Open-label, Crossover Study to Evaluate Bioequivalence Following a Single Oral Dose Administration of a Combination Tablet of SYR-322 and Metformin Hydrochloride in Healthy adult Male Subjects. In this study healthy subjects received either of the following treatments,

- Group A (n=16): Alogliptin 25 mg + Metformin 500 mg FDC Tablet (Test)
- Group B (n=16): Alogliptin 25 mg one tablet and two tablets of Metformin 250 mg (Reference)
Study IV was a Phase 1, Open-Label, Randomized, Crossover Study to Determine the Effects of Food on the Pharmacokinetics of a Fixed-Dose Combination of SYR-322 and Metformin Hydrochloride in Healthy Adult Subjects.

- Group A: Single dose of Alogliptin 12.5 mg + Metformin 500 mg FDC tablet in the Fed state (Test)
- Group B: Single dose of Alogliptin 12.5 mg + Metformin 500 mg FDC tablet in the Fasted state (Reference)

Study V was a Randomized, Open-label, Crossover Study to Determine the Effect of Food on the Pharmacokinetics of Single Oral Dose Administration of a Fixed-Dose Combination of SYR-322 and Metformin Hydrochloride in Healthy Adult Male Subjects.

- Group A: Single dose of Alogliptin 25 mg + Metformin 500 mg FDC tablet in the Fed state (Test)
- Group B: Single dose of Alogliptin 25 mg + Metformin 500 mg FDC tablet in the Fasted state (Reference)

Study I, II & III were evaluated bioequivalence and study IV and V were evaluated food effect of Alogliptin and Metformin fixed dose combination (FDC) tablet versus alogliptin and metformin individual tablets administered in healthy human subjects.

RESULTS

Study I:

Pharmacokinetic Results

- Cohort 1
  The 90% CIs for the ratios of the LS means for the AUC and Cmax values of both alogliptin (6.25 mg) and metformin (500 and 1000 mg) were within the 80% to 125% range. Therefore, the Alogliptin + Metformin FDC tablet FDC (6.25 mg + 500 mg and 6.25 mg + 1000 mg) tablets met the standards for bioequivalence to coadministration of the individual alogliptin 6.25 mg and metformin 500 and 1000 mg tablets.

- Cohort 2
  The 90% CIs for the ratios of the LS means for the AUC and Cmax values of both alogliptin (12.5 mg) and metformin (500 and 1000 mg) were within the 80% to 125% range. Therefore, the Alogliptin + Metformin FDC tablet FDC (12.5 mg + 500 mg and 6.25 mg + 1000 mg) tablets met the standards for bioequivalence to coadministration of the individual alogliptin 12.5 mg and metformin 500 and 1000 mg tablets.
Table 1: Safety and tolerability

<table>
<thead>
<tr>
<th>Table: 01</th>
<th>Study I</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort 1</td>
<td>Cohort 2</td>
</tr>
<tr>
<td>No. of Subjects had AE</td>
<td>16 (n=48)</td>
<td>17 (n=48)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Head ache</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Rhinorrhea</td>
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<td>0</td>
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<tr>
<td>Upper respiratory tract infection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
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<td>0</td>
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<tr>
<td>Epistaxis</td>
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<td>0</td>
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<tr>
<td>Blister</td>
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<tr>
<td>Back pain</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Dysgeusia</td>
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<td>0</td>
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<tr>
<td>Skin irritation</td>
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<td>0</td>
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<tr>
<td>Vessel puncture</td>
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<td>0</td>
</tr>
<tr>
<td>Site reaction</td>
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<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
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<td>0</td>
</tr>
<tr>
<td>Sunburn</td>
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<td>0</td>
</tr>
<tr>
<td>Presyncope</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total no. Of AE's</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>Related to study drug</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Not related to study drug</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Possibly related to study drug</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Probably related to study drug</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Definitely related to study drug</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

**Disposition of subjects**

| Recruited | 48 | 48 | 36 | 36 |
| Study Completed | 45 | 42 | 33 | 33 |
| Prematurely Discontinued | 3 | 6 | 3 | 3 |

**Discontinued due to**

| AE | 2 | 1 | 1 | 1 |
| Other reason | 1 | 1 | 1 | 0 |
| Protocol violation | 0 | 3 | 0 | 0 |
| Voluntarily withdrawn | 0 | 0 | 1 | 2 |

No deaths or serious adverse events occurred during the study. Overall, 2 subjects discontinued study drug due to adverse events. One subject discontinued due to an adverse event of anemia following treatment with Alogliptin + Metformin FDC tablet FDC (6.25 mg + 500 mg). The investigator considered the event...
mild in intensity and not related to study drug. One subject discontinued due to an adverse event of pyrexia following treatment with Alogliptin + Metformin FDC tablet FDC (12.5 mg + 500 mg). The investigator considered the event moderate in intensity and not related to study drug.

**Table 2: Study Design**

<table>
<thead>
<tr>
<th>Table 02</th>
<th>90% CI</th>
<th>Alogliptin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AUC(0-tlqc) (ng.hr/mL)</td>
<td>AUC(0-inf) (ng.hr/mL)</td>
</tr>
<tr>
<td>Study I</td>
<td>Treatment A vs B</td>
<td>104.80 (102.68, 106.96)</td>
<td>104.08 (102.13, 106.07)</td>
</tr>
<tr>
<td></td>
<td>Treatment C vs D</td>
<td>104.44 (102.34, 106.58)</td>
<td>104.34 (102.38, 106.33)</td>
</tr>
<tr>
<td></td>
<td>Treatment E vs F</td>
<td>98.50 (96.57, 100.46)</td>
<td>98.34 (96.38, 100.35)</td>
</tr>
<tr>
<td></td>
<td>Treatment G vs H</td>
<td>101.29 (99.29, 103.33)</td>
<td>100.69 (98.66, 102.77)</td>
</tr>
<tr>
<td>Study II</td>
<td>Treatment A vs B</td>
<td>0.9747-1.0272</td>
<td>0.9822-1.0301</td>
</tr>
<tr>
<td></td>
<td>Treatment C vs D</td>
<td>0.9628-1.0147</td>
<td>0.9665-1.0132</td>
</tr>
<tr>
<td></td>
<td>Treatment E vs F</td>
<td>0.9915-1.0282</td>
<td>0.9922-1.0275</td>
</tr>
<tr>
<td></td>
<td>Treatment G vs H</td>
<td>0.9951-1.0315</td>
<td>0.9961-1.0311</td>
</tr>
<tr>
<td>Study IV</td>
<td>Group A vs B</td>
<td>97.38 (92.27, 102.77)</td>
<td>95.75 (91.52, 100.18)</td>
</tr>
<tr>
<td>Study III</td>
<td>Group A vs B</td>
<td>0.999-1.027 AUC(0-72)</td>
<td>Nil</td>
</tr>
</tbody>
</table>
With the exception of the adverse event of anaemia, no clinically significant changes in clinical laboratory test results were reported. With the exception of the adverse event of pyrexia, no clinically significant changes in vital signs or ECG results were reported. No clinically significant changes from Baseline in a physical examination finding were noted.

Study II:

Pharmacokinetic results:

Following administration of alogliptin 6.25 mg and metformin 500 mg as an FDC tablet and as individual tablets, the 90% CIs for the point estimates of the ratios of the central values of the Cmax and AUCs of alogliptin and metformin were within the 0.80 to 1.25 bioequivalence range. Therefore, the Alogliptin + Metformin FDC tablet (6.25 mg + 500 mg) FDC tablet was bioequivalent to the individual tablets of alogliptin 6.25 mg and metformin 500 mg.

Following administration of alogliptin 6.25 mg and metformin 1000 mg as an FDC tablet and as individual tablets, the 90% CIs for the point estimates of the ratios of the central values of the Cmax and AUCs of alogliptin and metformin were within the 0.80 to 1.25 bioequivalence range. Therefore, the Alogliptin + Metformin FDC tablet (6.25 mg + 1000 mg) FDC tablet was bioequivalent to the individual tablets of alogliptin 6.25 mg and metformin 1000 mg.

Following administration of alogliptin 12.5 mg and metformin 500 mg as an FDC tablet and as individual tablets, the 90% CIs for the point estimates of the ratios of the central values of the Cmax and AUCs of alogliptin and metformin were within the 0.80 to 1.25 bioequivalence range. Therefore, the Alogliptin + Metformin FDC tablet (12.5 mg + 500 mg) FDC tablet was bioequivalent to the individual tablets of alogliptin 12.5 mg and metformin 500 mg.

Following administration of alogliptin 12.5 mg and metformin 1000 mg as an FDC tablet and as individual tablets, the 90% CIs for the point estimates of the ratios of the central values of the Cmax and AUCs of alogliptin and metformin were within the 0.80 to 1.25 bioequivalence range. Therefore, the Alogliptin + Metformin FDC tablet (12.5 mg + 1000 mg) FDC tablet was bioequivalent to the individual tablets of alogliptin 12.5 mg and metformin 1000 mg.

Safety and tolerability (Table 1):

No deaths or other serious adverse events occurred. Two subjects experienced adverse events leading to discontinuation of study drug. One subject discontinued study drug due to an adverse event of epistaxis following administration of Alogliptin + Metformin FDC tablet (6.25 mg + 500 mg), and 1 subject discontinued study drug due an adverse event of back pain following administration of individual tablets of alogliptin 12.5 mg and metformin HCl 1000 mg. Both events were considered by the investigator to be not related to study drug and moderate in intensity. No other significant adverse events occurred. Eight subjects had changes from Baseline in physical examination findings that were reported as adverse events; none of these adverse events were considered by the investigator to be related to study drug. No clinical laboratory test result, vital sign value, or ECG result was reported as an adverse event. No
pregnancies or overdoses occurred. No difference in safety profile was observed between the cohorts or among the treatment groups. Overall, no safety issues were identified in this study.

Study III:
Pharmacokinetic results (Table 2):

The two-sided 90% confidence intervals were within a range of ln (0.80) to ln (1.25) for both AUC(0-72) and Cmax, leading to the conclusion that combination tablet administration was bioequivalent to coadministration for Alogliptin, in accordance with the Bioequivalence Study Guideline.

The two-sided 90% confidence intervals were within a range of ln(0.80) to ln(1.25) for both AUC(0-48) and Cmax, leading to the conclusion that combination tablet administration was bioequivalent to coadministration for metformin, in accordance with the Bioequivalence Study Guideline.

Combination tablet administration was bioequivalent to coadministration for both alogliptin and metformin, demonstrating that the combination tablet was bioequivalent to coadministered active ingredient tablets.

Safety results:

The incidence of AEs was 9.4% (3/32 subjects) after combination tablet administration and 15.6% (5/32 subjects) after coadministration.

• The incidence of treatment-related AEs was 6.3% (2/32 subjects) after combination tablet administration and 3.1% (1/32 subjects) after coadministration.

• All AEs were mild in severity, and no SAEs or deaths were observed.

• No clinically significant changes were observed in vital signs, body weight, 12-lead ECG findings, or clinical laboratory test results.

Study IV:
Pharmacokinetic Results (Table 2):

The 90% confidence intervals for the ratios (fed/fasted) of the LS geometric means for AUC(0-tlqc) and AUC(0-inf) of alogliptin were contained entirely within the 80% to 125% range; however, the lower bound of the 90% confidence interval for Cmax of alogliptin extended slightly below 80%. The median Tmax of alogliptin was similar under fed and fasted conditions (P=0.263).

The 90% confidence intervals for the ratios (fed/fasted) of the LS geometric means for AUC(0-tlqc) and AUC(0-inf) of metformin were contained entirely within the 80% to 125% range. However, Cmax was decreased by approximately 28% under fed conditions and the 90% confidence interval extended below the 80% to 125% range. The median Tmax of metformin was delayed by approximately 1.5 hours under fed conditions compared with administration under fasted conditions. The difference in Tmax between regimens was statistically significant (P<0.001).

Safety and tolerability (Table 1):

The AE profile of Alogliptin + Metformin FDC tablet was similar when administered under fed or fasted conditions. Eleven of 24 subjects (45.8%) experienced 1 or more AEs during 1 or more treatment periods. Seven (29.2%) subjects experienced 1 or more AEs following both the fed and fasted treatment conditions.
regimens. Overall, the most commonly reported AEs were nausea (20.8%), diarrhea (12.5%), and headache (12.5%).

The majority of AEs were considered by the investigator to be related to study drug (26 of 31 events). Eight of 24 subjects (33.3%) experienced AEs that were considered by the investigator to be related to study drug. The majority of AEs were judged by the investigator to be mild in intensity (27 of 31 events). Four events (2 events each of nausea and vomiting) were judged to be of moderate intensity and all 4 events were considered related to study drug by the investigator.

No deaths, serious adverse events (SAEs), or other significant AEs occurred during the study. No laboratory test result, vital sign measurement, physical examination observation, or ECG result was reported as an AE.

Study V:
Pharmacokinetic Results (Table 2):

The 90% CIs for the difference in the log-transformed values of AUC(0-inf) between fed and fasted conditions were within the range of bioequivalence [between ln(0.80) and ln(1.25)]. Similar results were observed in AUC(0-48) AUC(0-tlqc). Cmax was approximately 15% lower under fed condition compared to fasted condition.

The mean cumulative urinary excretion ratios (SD) [% of dose] for metformin up to 48 hours after single administration of the SYR-322-MET tablet were 50.626% (7.6377) under fasted condition and 50.067% (7.6636) under fed condition, respectively. The mean CLr (SD) of metformin in each treatment was 27.88 L/hr (4.1525) under fasted condition and 28.34 L/hr (6.3364) under fed condition.

Pharmacodynamic Results:

The mean AUCs(0-24) (SD) of % inhibition rate of plasma DPP-4 activity following single administration of the SYR-322-MET tablet were 2114.62% inhibition·hr (30.355) under fasted condition and 2100.74% inhibition·hr (27.297) under fed condition, with mean Emax (SD) of 96.10% inhibition (1.022) and 96.33% inhibition (0.779), respectively. The median of Tmax was 3.000 hr under fasted condition and 1.000 hr under fed condition, respectively. The inhibition rate of DPP-4 activity was approximately 80% under both conditions at 24 hours after administration.

Safety and tolerability (Table 1):

- No TEAEs, including deaths, other SAEs, and other significant AEs occurred during the study.
- No clinically meaningful changes from baseline were noted in laboratory tests, vital signs, weight, or 12-lead ECG. No marked inter-treatment differences (fasted versus fed condition) were noted in these changes.

DISCUSSION

Alogliptin and Metformin in different strengths were administered and pharmacodynamic, pharmacodynamic; safety and tolerability were evaluated in healthy subjects in these 05 clinical trials.
The bioequivalence studies and food effect studies conducted in healthy subjects in five clinical trials with all of the strengths of alogliptin 6.25, 12.5 & 25 mg and metformin 500 & 1000 mg had no clinically meaningful drug interaction between the pharmacokinetics of either drug was observed suggesting that the two drugs could be combined into a single FDC tablet.

The present studies evaluated the bioequivalence of an IR FDC tablet of Alogliptin and metformin as compared to co-administration of individual single-component IR tablets at corresponding doses tablets of the individual components.

For all doses of alogliptin and metformin, the 90% CI for the test-to-reference LS of AUC and Cmax were close to 100% and entirely contained within the pre-specified bioequivalence limits of 80% to 125%. This indicates that the FDC tablet of alogliptin and metformin is bioequivalent to coadministration with respect to either alogliptin or metformin pharmacokinetics with no effects on its rate and extent of absorption as well as its elimination attributed to the formulation performance factors of the FDC tablet. The safety findings observed in these studies are consistent with those previously reported for concomitant administration of alogliptin (6.25, 12.5 & 25 mg) with metformin (500 & 1000 mg) in healthy subjects in which the incidence of the most prevalent TEAEs (gastrointestinal disorders) were more common with metformin alone as compared with alogliptin alone. Findings from 05 clinical trials in healthy subjects demonstrated favorable safety and tolerability of alogliptin when administered concomitantly with metformin with all doses.

CONCLUSIONS

The results of 05 bioequivalence and food effect studies in healthy subjects demonstrated that the pharmacokinetics of alogliptin and metformin across 03 dose levels are bioequivalent, and unaffected by formulation of the two components whether administered as an FDC tablet or co-administered as individual component IR tablets. Single doses of the alogliptin/metformin FDC tablet or the individual tablets of alogliptin and metformin in all strengths (6.25mg/500mg, 6.25 mg/1000mg, 12.5 mg/500 mg and 12.5 mg/1000 mg) were generally well-tolerated, other than gastrointestinal adverse events known to be associated with metformin. These results provide support for single dose administration of alogliptin and metformin FDC tablets in comparison with individual alogliptin and metformin tablets were bioequivalent, effective, safe and well tolerable in healthy subjects.

REFERENCES


