Dutogliptin, a selective DPP4 inhibitor, improves glycaemic control in patients with type 2 diabetes: a 12-week, double-blind, randomized, placebo-controlled, multicentre trial


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Aim: To determine efficacy and tolerability of dutogliptin, a dipeptidyl peptidase 4 (DPP4) inhibitor, in patients with type 2 diabetes mellitus.

Methods: This was a 12-week, multicentre, randomized, double-blind, placebo-controlled trial in 423 patients with type 2 diabetes with suboptimal metabolic control. Following a 2-week single-blind placebo run-in, patients aged 18–75 years with a body mass index of 25–48 kg/m² and baseline HbA1c of 7.3–11.0% were randomized 2:2:1 to receive once-daily oral therapy with either dutogliptin (400 or 200 mg) or placebo on a background medication of either metformin alone, a thiazolidinedione (TZD) alone or a combination of metformin plus a TZD.

Results: Average HbA1c at baseline was 8.4%. Administration of dutogliptin 400 and 200 mg for 12 weeks decreased HbA1c by −0.52% (p < 0.001) and −0.35% (p = 0.006), respectively (placebo-corrected values), with absolute changes in HbA1c for the 400 mg, 200 mg and placebo groups of −0.82, −0.64 and −0.3%, respectively. The proportion of patients achieving an HbA1c <7% was 27, 21 and 12% at dutogliptin doses of 400 and 200 mg or placebo, respectively (p = 0.008 for comparison of 400 mg vs. placebo). Fasting plasma glucose (FPG) levels were significantly reduced in both active treatment groups compared to placebo: the placebo-corrected difference was −1.00 mmol/l (p < 0.001) for the 400 mg group and −0.88 mmol/l (p = 0.003) for the 200 mg group. Dutogliptin caused significantly greater reductions in postprandial glucose AUC0–2h in both the 400 and 200 mg groups (placebo corrected values −2.58 mmol/l/h, p < 0.001 and −1.63 mmol/l/h, p = 0.032, respectively). In general, patients tolerated the study drug well. There were minor, not clinically meaningful differences in adverse events (AEs) between dutogliptin-treated patients and placebo controls, and 60% of all reported AEs were mild. Vital signs and body weight were stable, and routine safety laboratory parameters did not change compared with placebo. Trough ex vivo DPP4 inhibition at the end of the 12-week treatment period was 80 and 70%, at the 400 and 200 mg doses of dutogliptin, respectively.

Conclusions: Dutogliptin treatment for 12 weeks improved glycaemic control in patients with type 2 diabetes who were on a background medication of metformin, a TZD or metformin plus a TZD. Tolerability was favourable for both doses tested. The 400 mg dose of dutogliptin resulted in larger changes of HbA1c and FPG and more subjects reached an HbA1c target of <7% than the 200 mg dose.

Keywords: diabetes mellitus treatment, DPP4 inhibition, dutogliptin, HbA1c, incretins

Date submitted 1 November 2009; date of first decision 19 December 2009; date of final acceptance 21 December 2009

Introduction

Dutogliptin is a novel, orally available, potent and selective dipeptidyl peptidase-4 (DPP4) enzyme inhibitor. DPP4 is a serine protease that cleaves polypeptide substrates, including glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP increase insulin synthesis and release in response to food ingestion and decrease glucagon secretion in a glucose-dependent manner; these combined effects result in improved blood glucose control, primarily in the postprandial phase [1–3]. Continuous subcutaneous infusion of GLP-1 to patients with type 2 diabetes results in markedly improved glycaemic control [4]. In patients with type 2 diabetes, the endogenous GLP-1 response is blunted, leading to inappropriately reduced insulin secretion [5]. GLP-1 has a short half-life; therefore, strategies to inhibit the degradation of GLP-1 thereby enhancing its half-life have been developed in the last decade [6]. DPP4 inhibitors as well as GLP-1 analogues resistant to degradation by DPP4 are now available for the treatment of type 2 diabetic
patients, and additional compounds are currently in clinical development [1,7]. DPP4 inhibitors have the advantage of oral administration, lack of hypoglycaemia and absence of weight gain. DPP4 inhibitors improve glycaemic control, which ultimately should lead to a reduction of diabetic long-term complications.

Dutogliptin is highly water soluble (>2000 mg/ml), has low cellular permeability, exhibits low plasma protein binding (11%) and is rapidly absorbed with a 7max of 3–4 h and a half-life of 10–13 h. The compound is metabolically stable and does not inhibit or induce the activity of major CYP450s. The volume of distribution approximates the volume of extracellular body water and the excretion of dutogliptin occurs via passive renal filtration at the rate of glomerular filtration (data on file). These pharmacological properties are advantageous for a drug that is administered once daily and is targeted at DPP4, an enzyme located extracellularly [8].

Dutogliptin, formerly PHX1149, was tolerated well in earlier studies [9–10], and blood glucose control in diabetic subjects improved in a 4-week treatment study [10].

The 12-week study described here was conducted to compare the metabolic effects of two different dose levels of dutogliptin versus placebo in patients with type 2 diabetes with suboptimal metabolic control on a background of either metformin alone, a thiazolidinedione (TZD) alone or a combination of metformin plus a TZD.

Patients and Methods

Study Design

This was a multicentre, randomized, double-blind, placebo-controlled study conducted at 73 sites in the USA, Mexico, India, Canada and Argentina (Appendix). After a 2-week single-blind placebo run-in, patients were randomized 2:2:1 to receive dutogliptin tablets (400 or 200 mg) or matching placebo orally once daily in the morning with or without food for 12 weeks. Background therapy allowed during the study included metformin and/or TZD therapy. Prior to taking their first dose of double-blind study drug on day 1, patients ingested a standardized liquid test meal (2 cans of Ensure Plus, ∼720 cal, Abbott Laboratories). Serial blood samples for plasma glucose were collected over 2 h. The first dose of double-blind study drug was taken after the last postprandial blood sample was drawn. The primary outcome parameter was change in HbA1c from baseline (day 1) to day 84. Safety and tolerability were assessed throughout the study.

Study Population

To qualify for this study, patients had to be diagnosed with type 2 diabetes for >4 months but <12 years and had to have been taking metformin alone (≥1500 mg/day or highest tolerated dose), a TZD alone (any labelled dose) or a combination of metformin and a TZD. Doses of these antidiabetic agents had to be stable for at least 4 weeks (metformin) and 10 weeks (TZD) prior to study entry. At entry, male and non-pregnant female patients 18–75 years of age were required to have a body mass index (BMI) of 25–48 kg/m² (lower limit 23 kg/m² for patients from India), fasting plasma glucose (FPG) of 6.6–12.2 mmol/l, haemoglobin A1c (HbA1c) of 7.3–11.0% (upper limit ≤10.0 and 10.5% for Canada and Argentina, respectively) and a fasting plasma C-peptide >0.26 nmol/l. Patients were excluded if they had type 1, insulin-dependent type 2 or any rare form of diabetes mellitus; marked long-term diabetic complications; skin lesions or oedema; or history of hypoglycaemic episodes requiring second-party intervention within the previous 6 months.

Study Assessments

The primary efficacy variable was change in HbA1c from baseline at days 1 to 84 (12 weeks). Secondary variables included fasting and peak postprandial glucose, and percentage of patients achieving a HbA1c level of <7.0%. Ex vivo DPP4 inhibition (PD) and plasma dutogliptin levels (PK) were assessed also on day 84 during 2 h after study drug intake. In a subset of patients, PK and PD were evaluated 8 h after the last dose of study drug. Safety assessments included a complete physical examination and electrocardiogram (ECG) at screening and end of treatment visits. In addition, standard clinical laboratory tests (haematology, chemistry and urinalysis) were performed on a regular basis. Adverse events (AEs), vital signs and body weight were recorded at each visit. Patients were given diet and exercise counselling based on American Diabetes Association (ADA) guidelines [11] and instructed to measure and record blood glucose at home using home glucose meters.

Laboratory analyses used in the efficacy and safety evaluations were performed at regional central laboratories by either MDS Pharma Services, Mississauga, Ontario (for US and Canadian centers); Carpermor, Mexico City, Mexico; MDS Pharma Services, Singapore; or Laboratorio Hidalgo, Buenos Aires, Argentina. All laboratories used the same methodology for HbA1c, namely, the BioRad Variant method that is certified by the National Glycohemoglobin Standardization Program (NGSP). Dutogliptin plasma levels were assayed by LC/ESI/MS/MS at Charles River Laboratories, Shrewsbury, MA, using a validated analytical method. Pathway Diagnostics, Malibu, CA determined ex vivo DPP4 inhibition using a validated fluorometric assay and the synthetic substrate Gly-Pro-7-amino-4-methylcoumarin.

Analysis Populations and Data Analysis

In prior studies with other DPP4 inhibitors, the standard deviation of changes from baseline to the end of 3 months in HbA1c was up to ~1.0% [12]. Based on this standard deviation, 160 subjects in the dutogliptin 400 mg group and 80 subjects in the placebo group were expected to provide 95% power to detect an HbA1c difference of 0.5% in the mean change from baseline.

All efficacy analyses were conducted on the intention-to-treat (ITT) population, which included all randomized patients who received at least one dose of dutogliptin or placebo and had at least one postbaseline assessment. The primary endpoint was change in HbA1c from hours day 1 (baseline, day 1 of dosing) to day 84 or to the last available visit using
analysis of covariance (ANCOVA) with treatment and country as fixed factors and the baseline HbA1c as a covariate. Two-sided contrasts comparing each dutogliptin dose with the placebo group were assessed. Change from baseline in HbA1c at each postbaseline visit and change from baseline at each postbaseline visit in fasting and postprandial glucose were analysed as secondary endpoints using the last observation carried forward (LOCF) method. The change from days 1 to 84 in AUC0−2h and peak postprandial glucose was analysed with ANCOVA that included treatment and country as factors and the corresponding day 1 value as a covariate. Postprandial blood glucose on days 1 and 84 was assessed using an area under the curve (AUC) calculation. The proportion of patients achieving the target HbA1c level of ≤7.0% at day 84 was summarized by treatment and the difference among treatment groups was assessed using the Cochran–Mantel–Haenszel test stratified by country. All statistical testing was completed at α = 0.05 level of significance. All efficacy data are expressed as the least square means ± s.e.m.

Mean dutogliptin plasma concentrations over the 24-h dosing interval were calculated by nominal sampling time, with the 24-h concentration values on day 85 set equal to the predose trough concentration on day 84. Statistical analysis of pharmacokinetic parameters was performed using analysis of variance (ANOVA). The per cent DPP4 inhibition at day 84 was summarized by treatment and the difference among treatment groups was assessed using the Cochran–Mantel–Haenszel test stratified by country. All statistical testing was completed at α = 0.05 level of significance. All efficacy data are expressed as the least square means ± s.e.m.

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The safety population included all patients who received at least one dose of double-blind study drug and had at least one postbaseline safety assessment. AEs were coded using The Medical Dictionary for Regulatory Activities (MedDRA) coding system.

**Ethics and Good Clinical Practice**

The protocol was approved by the independent ethics committee and/or institutional review board at each study centre. All patients gave written informed consent to participate prior to the performance of any study procedures. The trial was conducted according to ethical principles that originate in the Declaration of Helsinki and was consistent with Good Clinical Practice guidelines and local regulatory requirements of the USA, Canada, Mexico, Argentina and India.

**Results**

**Patients**

A total of 423 patients were randomized, and 422 patients comprised both the ITT and safety populations. Patient disposition is shown in figure 1. Overall, 376 patients (89%) completed the 12-week double-blind dosing period. The patient characteristics were well balanced among treatment groups (Table 1). Patients on average were 53-years old. In the different dose groups, the mean BMI was 31–32 kg/m², 50–55% were Caucasian, 23–24% were Asian and 5–7% was African American; Hispanics/Latinos represented 38–43% of the entire study population. Background therapy for the majority of patients (74–78%) was metformin monotherapy, and 20–22% were taking a combination of metformin and a TZD. Participants had a mean baseline HbA1c of 8.4% and a mean fasting glucose of 9.62 mmol/l on day 1, the start of double-blind study drug dosing.

**Efficacy**

The study met its primary and secondary efficacy endpoints. HbA1c decreased in a dose-dependent manner with dutogliptin treatment. The placebo-corrected changes in HbA1c from days 1 to 84 were −0.52% (p < 0.001) and −0.35% (p = 0.006) for the dutogliptin 400 and 200 mg groups, respectively (figure 2a). The absolute change in HbA1c from days 1 to 84 for the 400 mg, 200 mg and placebo groups were −0.82, −0.64 and −0.30%, respectively. Analyses of the secondary endpoints also showed efficacy of dutogliptin relative to placebo. A significantly greater proportion of patients achieved an HbA1c <7% in the 400 mg group (27%, p = 0.008) compared with placebo (12%). The proportion of patients achieving an HbA1c <7% was smaller in the 200 mg group (21%, p = 0.056) (figure 2b). None of the subgroup analyses (age, race, ethnicity, background therapy, BMI, baseline HbA1c (%) or country) showed a statistically significant interaction with the treatment group, indicating the effects of dutogliptin were comparable regardless of these characteristics. Subjects who started with a HbA1c >8.5% showed a larger absolute decrease from baseline compared with those who had a HbA1c of ≤8.5% (−1.06 vs. −0.61% at the 400 mg dose, −0.86 vs. −0.46% at the 200 mg dose and −0.36 vs. −0.19% in the placebo group). In a prespecified analysis, the effects on HbA1c by country were analysed. A placebo effect was observed in patients from Mexico that was markedly greater than in patients from all other countries; therefore, change in HbA1c (%) was analysed excluding data from this country in a post hoc analysis: The placebo-corrected differences in mean change from days 1 to 84 excluding Mexico were statistically significant: −0.67% (p < 0.001) and −0.46% (p < 0.001) in the 400 and 200 mg groups, respectively. The absolute changes in HbA1c from days 1 to 84 were −0.83 and −0.62% for the 400 and 200 mg groups, respectively.

Changes from days 1 to 84 in FPG levels were significantly reduced in both active treatment groups at day 84 compared with placebo: the placebo-corrected difference was −1.00 mmol/l (p < 0.001) for the 400 mg group and −0.88 mmol/l (p = 0.003) for the 200 mg group (figure 2c). In addition, dutogliptin caused significantly greater placebo-corrected reductions in postprandial glucose AUC0−2 in both the 400 and 200 mg groups (−2.58 mmol/l/h, p < 0.001; −1.63 mmol/l/h, p = 0.032, respectively) from days 1 to 84 (figure 2d). Similarly, a significant decrease in peak blood glucose was seen in the 400 and 200 mg groups (−1.60 mmol/l, p < 0.001; −1.07 mmol/l, p = 0.017, respectively, placebo-corrected values).

**Weight**

Patients in both active treatment groups and placebo exhibited a similar, small mean weight loss over the 12 weeks of the dosing period. The mean decrease at day 84 compared to baseline was...
Screened for eligibility \( (n = 858) \)

Excluded \( (n = 435) \)
- Failed screening \( (n = 415) \)
- Dropped from single-blind run-in \( (n = 20) \)

Total randomized \( (n = 423) \)

Assigned to:
- Placebo \( (n = 86) \)
  - Treated per protocol \( (n = 71) \)
  - ITT population \( (n = 86) \)
  - Safety population \( (n = 86) \)

Assigned to:
- DUTOGLIPTIN 200 mg daily \( (n = 175) \)
  - Treated per protocol \( (n = 146) \)
  - ITT population \( (n = 174) \)
  - Safety population \( (n = 174) \)

Assigned to:
- DUTOGLIPTIN 400 mg daily \( (n = 162) \)
  - Treated per protocol \( (n = 138) \)
  - ITT population \( (n = 162) \)
  - Safety population \( (n = 162) \)

Did not complete
- Adverse event \( (n = 0) \)
- Death \( (n = 0) \)
- Withdrew consent \( (n = 2, 2.3\%) \)
- Protocol violation \( (n = 0) \)
- Lost to follow-up \( (n = 4, 4.7\%) \)
- Unacceptable metabolic control \( (n = 2, 2.3\%) \)
- Investigator discretion \( (n = 2, 2.3\%) \)
- Sponsor decision \( (n = 0) \)
- Other \( (n = 1, 1.2\%) \)

Completed * \( (n = 74, 86.0\%) \)

Did not complete
- Adverse event \( (n = 2, 1.1\%) \)
- Death \( (n = 0) \)
- Withdrew consent \( (n = 6, 3.4\%) \)
- Protocol violation \( (n = 2, 1.1\%) \)
- Lost to follow-up \( (n = 1, 0.6\%) \)
- Unacceptable metabolic control \( (n = 2, 1.1\%) \)
- Investigator discretion \( (n = 3, 1.7\%) \)
- Sponsor decision \( (n = 3, 1.7\%) \)
- Other \( (n = 1, 0.6\%) \)

Completed \( (n = 155, 88.6\%) \)

Did not complete
- Adverse event \( (n = 1, 0.6\%) \)
- Death \( (n = 0) \)
- Withdrew consent \( (n = 5, 3.1\%) \)
- Protocol violation \( (n = 0) \)
- Lost to follow-up \( (n = 0) \)
- Unacceptable metabolic control \( (n = 5, 3.1\%) \)
- Investigator discretion \( (n = 2, 1.2\%) \)
- Sponsor decision \( (n = 0) \)
- Other \( (n = 1, 0.6\%) \)

Completed * \( (n = 147, 90.7\%) \)

**Figure 1.** Disposition of study patients from screening through end of study. ITT, intention-to-treat. *Two patients had missing data, one placebo patient had a missing field for study completion but completed the study, and one patient in the 400 mg group did not have an end of study form but completed the day 1 visit.

0.23, 0.36 and 0.10 kg for the 400 and 200 mg dutogliptin and placebo dose groups, respectively. These changes were not statistically significant and indicate weight neutrality of dutogliptin.

**Pharmacokinetics**

Following dosing on day 84, mean plasma concentrations of dutogliptin increased rapidly and in a dose-dependent fashion (figure 3) reaching highest mean concentrations of approximately 210 ng/ml and 140 ng/ml at 2 h for the 400 and 200 mg groups respectively. Dutogliptin plasma levels gradually and slowly declined to trough levels of approximately 45 and 30 ng/ml in the 400 and 200 mg groups, respectively; this indicates a narrow peak-to-trough concentration range.

**Pharmacodynamics**

The mean per cent *ex vivo* DPP4 inhibition measured prior to dosing (trough) on day 84 was 80 and 70% relative to baseline for the 400 and 200 mg groups, respectively. After drug intake on the morning of day 84, mean DPP4 inhibition increased rapidly, reaching maximum inhibition of 93 and 90%, respectively, at 3 h and declining only slightly by the 8 h time point to 91 and 88%, respectively, in the 400 and 200 mg dose groups.

**Safety and Tolerability**

Of the total of 422 patients treated, 217 (51.4%) reported one or more AEs. A slightly higher number of patients in the placebo group (55.8%) experienced AEs compared with the dutogliptin groups (50.6 and 50.0% in the 400 and 200 mg dose groups, respectively). The majority of events were unrelated to study treatment; 7.8% of all patients reported at least one treatment-related AE. All treatment-related AEs were either mild or moderate in severity; none were severe (tables 2). The overall reported frequency of AEs was low across all treatment groups; the most commonly
Table 1. Demographics and disease characteristics of the ITT population.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (N = 86)</th>
<th>Dutogliptin dose groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>200 mg (N = 174)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± s.d.</td>
<td>53 ± 11</td>
<td>53 ± 10</td>
</tr>
<tr>
<td>Range</td>
<td>20–80</td>
<td>24–76</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (52.3)</td>
<td>93 (53.4)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (47.7)</td>
<td>81 (46.6)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>47 (54.7)</td>
<td>93 (53.4)</td>
</tr>
<tr>
<td>African American</td>
<td>6 (7.0)</td>
<td>9 (5.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>20 (23.3)</td>
<td>41 (23.6)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (15.1)</td>
<td>31 (17.8)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>33 (38.4)</td>
<td>67 (38.5)</td>
</tr>
<tr>
<td>Non-Hispanic/Non-Latino</td>
<td>53 (61.6)</td>
<td>107 (61.5)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± s.d.</td>
<td>31.7 ± 5.8</td>
<td>31.7 ± 5.6</td>
</tr>
<tr>
<td>Range</td>
<td>23.2–47.7</td>
<td>23.0–47.3</td>
</tr>
<tr>
<td><strong>Enrollment, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argentina</td>
<td>5 (5.8)</td>
<td>11 (6.3)</td>
</tr>
<tr>
<td>Canada</td>
<td>14 (16.3)</td>
<td>19 (10.9)</td>
</tr>
<tr>
<td>India</td>
<td>18 (20.9)</td>
<td>39 (22.4)</td>
</tr>
<tr>
<td>Mexico</td>
<td>20 (23.3)</td>
<td>41 (23.6)</td>
</tr>
<tr>
<td>USA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA—small centres</td>
<td>16 (18.6)</td>
<td>37 (21.3)</td>
</tr>
<tr>
<td>USA—large centres</td>
<td>13 (15.1)</td>
<td>28 (16.1)</td>
</tr>
<tr>
<td><strong>Baseline HbA1c (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± s.d.</td>
<td>8.4 ± 1.1</td>
<td>8.5 ± 1.0</td>
</tr>
<tr>
<td>Range</td>
<td>6.0–11.3</td>
<td>6.2–11.6</td>
</tr>
<tr>
<td><strong>Background, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin ≥1500 mg</td>
<td>67 (77.9)</td>
<td>129 (74.1)</td>
</tr>
<tr>
<td>TZD alone</td>
<td>2 (2.3)</td>
<td>8 (4.6)</td>
</tr>
<tr>
<td>Metformin + TZD</td>
<td>17 (19.8)</td>
<td>37 (21.3)</td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>9 (10.5)</td>
<td>19 (10.9)</td>
</tr>
</tbody>
</table>

Race, ‘Other’ includes native American, Alaska native, native Hawaiian or other Pacific islander, or other. BMI, body mass index; HbA1c, haemoglobin A1c; large centers, ≥10 subjects; small centers, <10 subjects; TZD, thiazolidinedione.

reported events were urinary tract infection (4.3%), diarrhoea (3.6%), headache (3.3%) and upper respiratory tract infection (URI) (3.6%). Slightly more AEs of headache (4.3%), arthralgia (3.7%), sinusitis (3.7%) and dizziness (2.5%) occurred in the 400 mg dose group when compared with placebo (1.2–3.5%). The incidence of URI was higher in the placebo group (5.8%) compared with the dutogliptin groups (2.3–3.7%). Similarly, gastrointestinal disorders were somewhat higher in the placebo group (12.8%) compared with the dutogliptin groups (10.7%). Overall, the few imbalances between the active treatment groups and placebo were small.

Five patients reported AEs of hypoglycaemia, one in the placebo, three in the 200 mg and one in the 400 mg dose group. No blood glucose values for these events were available, and no third party intervention was required. Two additional reports (one in each active dose group) were based on laboratory values without symptoms.

Four serious adverse events (SAEs) occurred during the double-blind period, two (2.3%) in the placebo group (ischaemic stroke and exacerbation of asthma) and one each in the 200 and 400 mg dutogliptin groups (emphysema/pneumonia and oesophagitis/gastritis, respectively). None of the SAEs were considered related to study drug. Discontinuations because of AEs occurred in two patients (1.1%) in the 200 mg group (hyperglycaemia, angioedema) and one patient (0.6%) in the 400 mg group (dizziness). The patient who was discontinued in the 200 mg group experienced angioedema and urticaria in the first week of dutogliptin therapy. This was a 57-year-old African American male who had been on concomitant therapy with lisinopril for approximately 2 years prior to entry into the study.

There were no meaningful differences in clinical laboratory parameters (including lipid levels), physical examination findings (including targeted physical exam as mandated by the FDA for oedema, skin observations and lymph nodes), vital signs and ECG parameters in either of the dutogliptin treatment groups compared with placebo.
Figure 2. (a) Change in HbA1c (%) from days 1 to 84, (b) change in HbA1c (%) from days 1 to 84 for subjects with HbA1c of >8.5% or ≤8.5% on day 1, (c) Change in HbA1c over time by visit, (d) Change in fasting plasma glucose (FPG) (mg/dl) days 1 to 84, and (e) Change in AUC (0–2 h) (mmol/l*h) of postprandial glucose from baseline prior to study drug administration to day 84, the last day of double-blind dosing. All values are least square means ± s.e.m., p versus placebo.

Discussion

Dutogliptin administered for 12 weeks at once-daily doses of 400 and 200 mg was well tolerated. Difference in AEs between the dutogliptin-treated patients and the placebo control patients were small.

Statistically significant dose-dependent reductions of HbA1c, the proportion of patients reaching an HbA1c target of <7%, and reduction of fasting blood glucose were noted. Effects on FPG were rapid and occurred during the first 2–3 weeks. The HbA1c response was continual and did not appear to plateau at the end of the 12-week treatment period. Trough DPP4 inhibition at the end of the 12-week treatment period was 80 and 70% with the 400 and 200 mg doses of dutogliptin, respectively. This extent of enzyme inhibition has been found to be effective in producing clinically meaningful improvements in glycaemic control with other DPP4 inhibitors [13–15]. Based on the common mechanism of action, which is enhancement of incretin effects, clinical studies of comparable duration with other DPP4 inhibitors have shown very similar efficacy results [for reviews see 12,16]. The mechanism of all incretin-based therapies is blood glucose dependent with best efficacy obtained when blood glucose levels are high [1]. This is exemplified by our finding that those subjects who had a baseline HbA1c >8.5% had a greater glycaemic response than those who started with an HbA1c ≤8.5%. Dutogliptin did not show any weight gain and the incidence of hypoglycaemia was low.
Nasopharyngitis has been consistently reported as a drug-related adverse event with other DPP4 inhibitors, including sitagliptin, vildagliptin, alogliptin and saxagliptin [12,17–20]. Of interest, in our study, nasopharyngitis was observed somewhat less frequently in the dutogliptin-treated subjects compared to the placebo-treated subjects; the same observation was made in a previous study with dutogliptin [10]. It has been suggested that nasopharyngitis may be mediated by physiological DPP4 substrates other than GLP-1, such as proinflammatory mediators (e.g. Substance P and other neurokinins) [21–23]. Dutogliptin is highly soluble in water (>2000 mg/ml), hydrophilic in nature, and, based on its low volume of distribution, thought to be located in the extracellular compartment. These properties of dutogliptin are probably the explanation for the observed low cellular permeability and limited tissue distribution (manuscript in preparation). These features could minimize any undesired off-substrate effects, such as modulation of non-incretin DPP4 substrates like Substance P, which may require tissue localization of a DPP4 inhibitor. The labels for both DPP4 inhibitors currently approved in the United States include hypersensitivity reactions (sitagliptin: anaphylaxis, angioedema, Stevens Johnson syndrome; saxagliptin: urticaria, facial oedema) [19,20]. In the present study, no increase in skin AEs was observed.

In summary, once-daily administration of dutogliptin for 12 weeks was effective in improving glycaemic control as measured by HbA1c, FPG and postprandial plasma glucose. Dutogliptin was well tolerated and no clear drug-associated profile of AEs emerged. The 400 mg dose of dutogliptin is currently being evaluated in a series of longer-term registration studies.

Acknowledgements
This study was funded by Phenomix Corporation. The authors thank the patients, investigators and participating staff at all clinical sites. Furthermore, we wish to thank MDS Pharma Services, Inc and Diagnosearch Life Sciences.
for field monitoring, data management, and statistical analysis. Dr Howard Foyt conducted a critical review of the manuscript.

**Appendix**

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**References**


