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MONOGRAPH

DUTOGLIPTIN TARTRATE

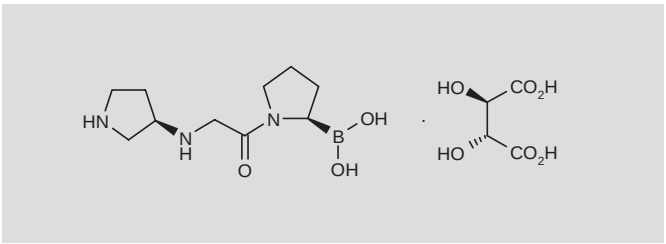
Rec INNM; USAN

Dipeptidyl Peptidase 4 Inhibitor
Treatment of Diabetes

PHX-1149

1-[*N*-[3(*R*)-Pyrrolidinyl]glycyl]pyrrolidin-2(*R*)-ylboronic acid L-tartrate

InChI: 1S/C10H20BN3O3.C4H6O6/c15-10(7-13-8-3-4-12-6-8)14-5-1-2-9(14)11(16)17;5-1(3(7)8)2(6)4(9)10/h8-9,12-13,16-17H,1-7H2;1-2,5-6H,(H,7,8)(H,9,10)/t8-,9+;1-,2-/m11/s1



$C_{10}H_{20}BN_3O_3.C_4H_6O_6$
Mol wt: 391.182
CAS: 890402-81-0
CAS: 852329-66-9 (free base)
EN: 386447

SUMMARY

Following consumption of a meal, plasma glucose levels are managed by insulin and glucagon release. The postprandial release of insulin and glucagon is regulated by the incretin hormones glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide (GIP), which are rapidly inactivated by the action of dipeptidyl peptidase 4 (DPP IV) proteases. Postprandial levels of the incretin hormones are severely reduced in patients with type 2 diabetes, leading to compromised plasma glucose homeostasis. Preventing inactivation of incretin hormones in order to increase their postprandial duration of action should have potential in the management of diabetes. With this in mind, a number of DPP IV inhibitors have been prepared and shown to successfully lower glycated hemoglobin levels and correct fasting plasma glucose concentrations in patients with type 2 diabetes. Dutogliptin tartrate is a small soluble DPP IV inhibitor that was developed by Phenomix and is currently in phase II/III clinical trials as monotherapy or in combination with other existing treatments for the management of type 2 diabetes.

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*Synthesis prepared by R. Pandian, J. Bolòs, R. Castañer. Thomson Reuters, Provença 388, 08025 Barcelona, Spain.

SYNTHESIS*

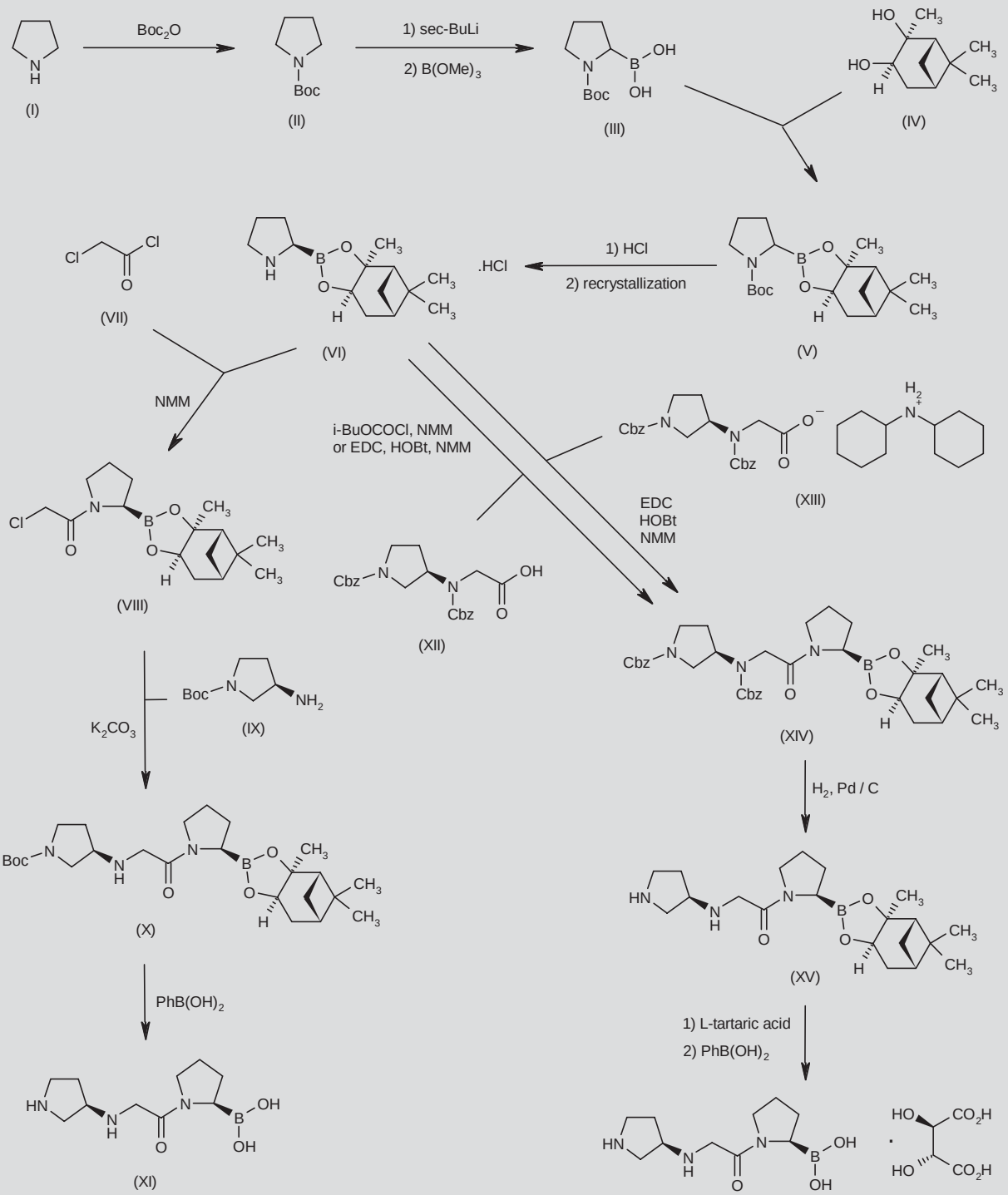
Dutogliptin and its tartrate salt can be synthesized by the following methods:

Protection of pyrrolidine (I) with Boc_2O in MTBE provides the corresponding *N*-Boc derivative (II) (1), which after metalation with *sec*-BuLi in THF and quenching with $B(OMe)_3$ gives *N*-Boc-boroproline (III) (1-3). Condensation of racemic boronic acid (III) with (+)-pinanediol (IV) in isopropyl acetate (1) or MTBE (2, 3) affords the boronate ester (V) as a diastereomeric mixture. After deprotection by removing the Boc group with HCl in *i*-PrOH (1) or Et_2O (2, 3), the 2(*R*)-boroproline pinanediol ester hydrochloride (VI) diastereomer is separated by recrystallization from *i*-PrOH (1-3). Acylation of compound (VI) with 2-chloroacetyl chloride (VII) in the presence of NMM in CH_2Cl_2 provides the 2-chloroacetamide (VIII), which is then condensed with 3(*R*)-amino-1-Boc-pyrrolidine (IX) by means of K_2CO_3 in THF to give the glycinamide derivative (X). Finally, simultaneous hydrolysis of the *N*-Boc and boronate ester groups in compound (X) using phenylboronic acid in H_2O/hexane provides dutogliptin free base (XI) (2, 3). Scheme 1.

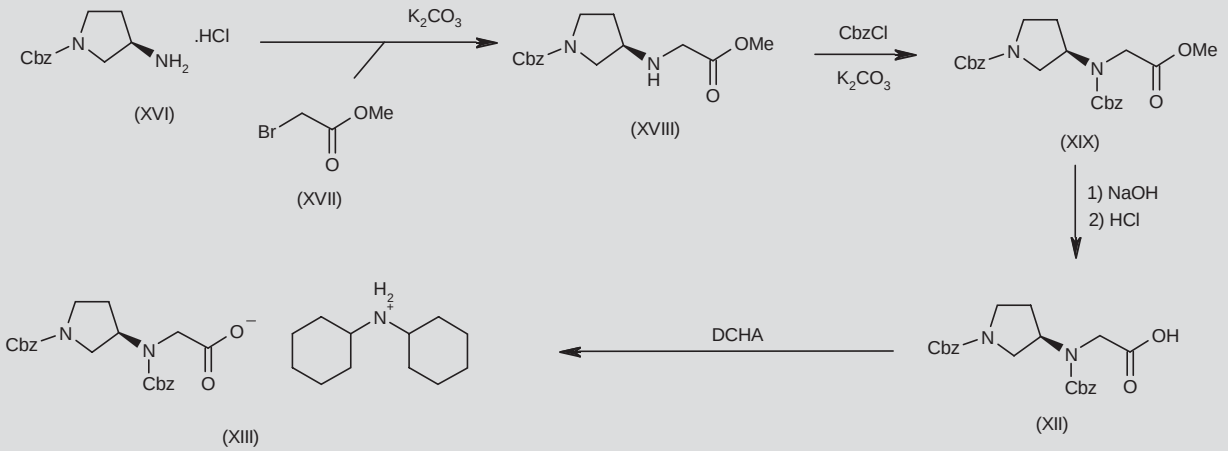
Alternatively, coupling of the 2(*R*)-boroproline derivative (VI) with either the diprotected *N*-(benzyloxycarbonyl)-*N*-[1-(benzyloxycarbonyl)-3(*R*)-pyrrolidinyl]glycine (XII) via activation as the corresponding mixed anhydride with isobutyl chloroformate and NMM in 2-MeTHF (1, 4), or by means of EDC, HOBt and NMM in CH_2Cl_2 (5), or also with the dicyclohexylamine salt (XIII) in the presence of EDC, HOBt and NMM (6, 7), affords amide (XIV), which is deprotected by catalytic hydrogenolysis over Pd/C in MeOH to give diamine (XV). Finally, diamine (XV) undergoes boronate ester cleavage by means of phenylboronic acid in the presence of L-tartaric acid in H_2O/MTBE to afford dutogliptin tartrate (1, 4-7). Scheme 1.

The precursors *N*-(benzyloxycarbonyl)-*N*-[1-(benzyloxycarbonyl)-3(*R*)-pyrrolidinyl]glycine (XII) and its dicyclohexylamine salt (XIII) are prepared as follows. Alkylation of 3(*R*)-amino-1-(benzyloxycarbonyl)pyrrolidine or its hydrochloride (XVI) with methyl 2-bromo-

Scheme 1. Synthesis of Dutogliptin and Dutogliptin Tartrate



Scheme 2. Synthesis of Precursors (XII) and (XIII)



acetate (XVII) by means of K_2CO_3 in MTBE/H_2O yields the amino ester (XVIII), which, without isolation, is further protected with benzyloxycarbonyl chloride to provide the diprotected compound (XIX). Hydrolysis of the methyl ester (XIX) with NaOH in refluxing MTBE/H_2O followed by in situ treatment of the obtained sodium salt with HCl leads to the carboxylic acid (XII) (1, 4, 6, 7), which by treatment with dicyclohexylamine in THF provides the corresponding dicyclohexylammonium salt (XIII) (6, 7). Scheme 2.

BACKGROUND

The homeostasis of plasma glucose levels is achieved by the coordinated regulation of glucagon and insulin secretion, with insulin promoting postprandial glucose clearance and storage as glycogen, and glucagon acting reciprocally to promote glycogen metabolism during fasting. Following the consumption of a meal, the glucose-dependent incretin hormones glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide/glucose-dependent insulinotropic polypeptide (GIP) act on pancreatic islet cells to maintain glucose homeostasis. GLP-1 is released from the L-cells of the ileum and colon and plays a role in increasing insulin secretion, suppressing glucagon release, slowing gastric emptying, increasing satiety, promoting β-cell neogenesis and inhibiting apoptosis (8, 9) (Fig. 1). GIP is released by K-cells of the intestine (8, 10) and is involved in glucose clearance and stimulates glucagon release following a meal. The action of the incretin hormones is rapidly halted within minutes by degradation via the action of dipeptidyl peptidase 4 (DPP IV or CD26), a family of ubiquitous serine proteases, which can also have secondary actions on other active peptides, such as substance P (11, 12). The DPP IV family members include four enzymes –DPP IV (expressed in a soluble circulating form and a cell membrane-bound form), seprase (FAP), DPP8 and DPP IX (both cytoplasmic)– and two non-enzymes –DPP VI and DPP X. With the exception of DPP IV, little is known about the endogenous substrates for the other family members (13).

Studies in animal models of diabetes have highlighted the importance of the incretins in maintaining plasma glucose levels. GLP-1 receptor knockout mice were glucose-intolerant and exhibited compromised insulin secretion in response to oral glucose (14). In addition, GLP-1 and GIP receptor antagonists have been shown to increase glucose intolerance in animal models (15-17). Furthermore, murine *DPP4* gene knockouts displayed improved glucose tolerance and higher circulating levels of insulin (18).

In patients with type 2 diabetes, although it retains physiological activity, the circulating level of postprandial GLP-1 is significantly reduced, as is pancreatic β-cell mass (insulin release), while β-cell (glucagon release) mass is increased (19). Moreover these patients show a blunted response to i.v. administration of GLP-1 (20). Conversely, the level of circulating GIP is not reduced; however, the robustness of the response to GIP is affected (21). Treatment with currently approved DPP IV inhibitors such as sitagliptin (Januvia™; Merck & Co.) has been shown to increase the ratio of active postprandial incretins in the circulation, decrease the level of glycated hemoglobin A_{1c} (HbA_{1c}, a marker of type 2 diabetes) and increase the plasma half-life ($t_{1/2}$) of GLP-1, helping to maintain normal postprandial glycemic control (22). Existing DPP IV inhibitors display a low incidence of adverse events (AEs), and are effective when used as monotherapy or in combination with other antidiabetic therapies such as metformin, thiazolidinediones and insulin (11). The attractiveness of employing DPP IV inhibitors in treating type 2 diabetes as compared to existing therapies includes: a low risk of hypoglycemia due to the need for glucose to be present, a null effect on body weight changes, good specificity of the drug in targeting DPP IV as opposed to other family members, and the potential for correcting the α/β-islet cell ratio, although the latter has only been observed in animal models.

Dutogliptin tartrate, an orally available, small-molecule DPP IV inhibitor, was developed by Phenomix and is currently undergoing phase II/III clinical trials for the treatment of type 2 diabetes as monotherapy or in combination with other type 2 diabetes management therapies.

PRECLINICAL PHARMACOLOGY

Dutogliptin is a small (241.16 Da), highly water-soluble (> 2 g/mL), orally active molecule that displays greater specificity for DPP IV

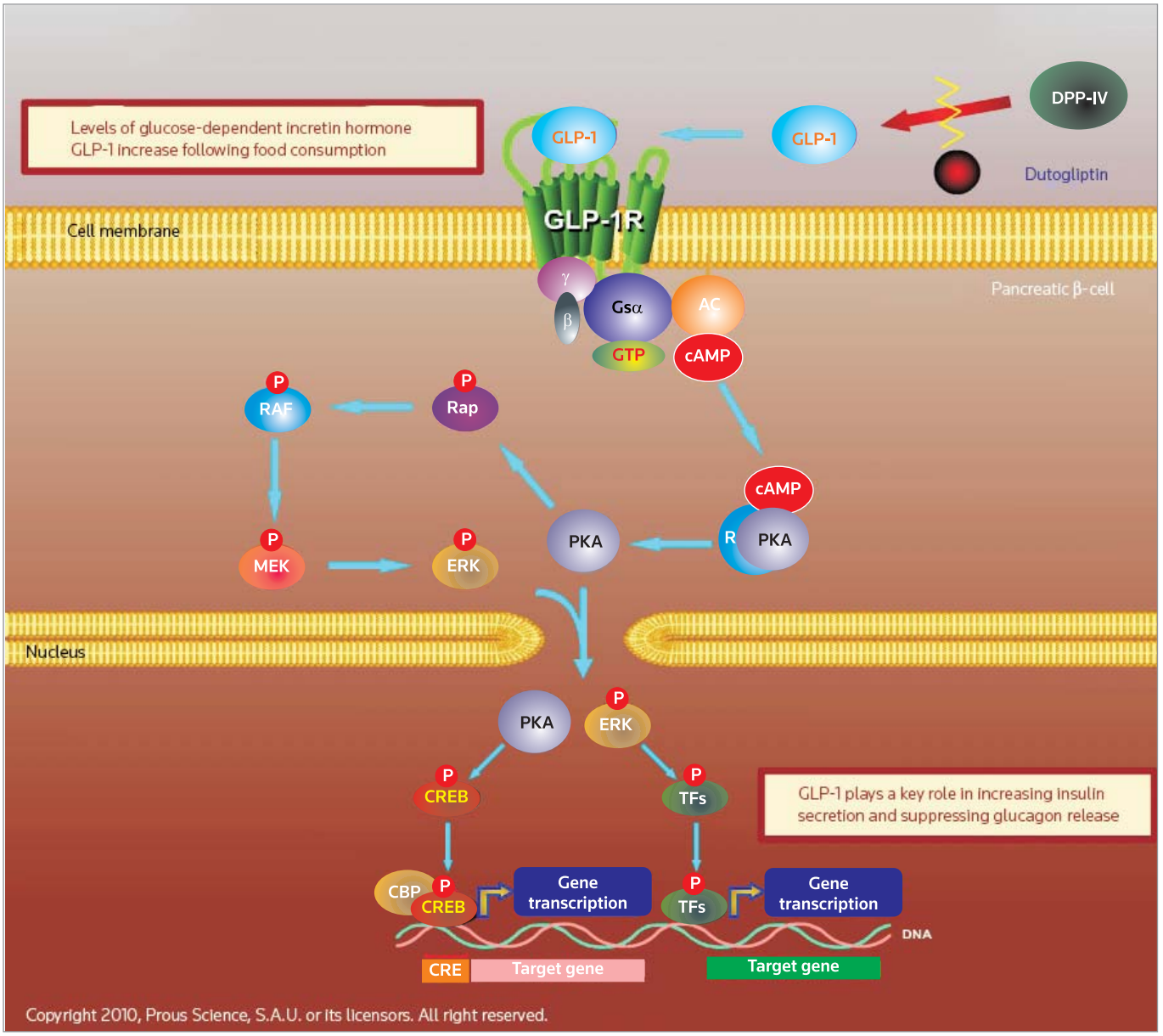


Figure 1. Dutogliptin - a dipeptidyl peptidase 4 (DPP IV) inhibitor. AC, adenylate cyclase, TFs, transcription factors.

(IC_{50} = 25 nM) than for other DPP family members, showing selectivity over DPP II and DPP IX (> 15 times), and over DPP8 and seprase (> 200 times) (23, 24). Dutogliptin exhibited dose-dependent inhibition of DPP IV activity (1-10 mg/kg/day) with a low peak to trough plasma concentration versus time curve and a $t_{1/2}$ of approximately 4 and 6 h, respectively, in rats and monkeys. In monkeys, dutogliptin (15 mg/kg/day) showed a 90% and > 50% reduction in DPP IV activity when assessed at 12 and 24 h postadministration. Treatment of wild-type C57Bl/6J and diabetic *ob/ob* mice with dutogliptin improved animal response in acute glucose tolerance tests, effectively decreasing peak glucose excursion and markedly increasing incretin GLP-1 and insulin levels. In rodents, dutogliptin demonstrated low protein binding, high aqueous solubility and a low volume of distribution, and was found to be metabolically stable, cleared via the kidneys and to demonstrate a favorable safety profile (24, 25).

PHARMACOKINETICS AND METABOLISM

The pharmacokinetic/pharmacodynamic profile of dutogliptin was assessed in humans in both single- and multiple-dose studies. In the single-dose study, 30 healthy patients (47% male; mean age = 51 ± 10 years) were given a single oral dose of dutogliptin (50-500 mg) or placebo. In the multiple-dose study, 28 healthy patients (57% male; mean age = 51 ± 12 years) were given dutogliptin (50-400 mg/day) or placebo for 13 days. Following administration of dutogliptin, dose-

dependent increases in mean peak plasma concentration (C_{max}) ranged from 25.8 to 741 ng/mL in the single-dose study (50-500 mg) and from 33.7 to 385, 36.1 to 287 and 33.4 to 215 ng/mL, respectively, on days 1, 7 and 13 in the multiple-dose cohort (50-400 mg/day). The time to reach peak plasma concentration (t_{max}) ranged from 2 to 4 h in both cohorts and $t_{1/2}$ ranged from 10 to 13 h as assessed in the single-dose cohort. The area under the curve (AUC) also increased in a dose-dependent fashion. At 24 h the level of DPP IV inhibition in volunteers receiving multiple doses > 100 mg was > 50%, rising to approximately 90% in volunteers who received a dose of 400 mg. A linear relationship was seen between plasma concentrations of dutogliptin and DPP IV inhibition, with EC_{50} and EC_{90} values of approximately 10 and 100 ng/mL, respectively. This study concluded that a daily dose of dutogliptin could be well tolerated across all patients, with limited AEs (23, 26).

A similar assessment was made in healthy nondiabetic obese or overweight volunteers (age range = 18-60 years; body mass index [BMI] = 27-35 kg/m^2) who were treated with dutogliptin in a single-escalating-dose study (50-500 mg). At each dose level five volunteers received dutogliptin and one received placebo. The t_{max} and $t_{1/2}$ ranged from 2.8 to 4.8 h and from 9.4 to 12.0 h, respectively, indicating that steady state should be attained within 2-3 days. C_{max} was correlated with increasing dose and ranged from 27 ng/mL at the lowest dose (50 mg) to 1821 ng/mL at the highest dose (500 mg). AUC also increased in a dose-dependent manner. The ex vivo inhibition of DPP IV was highest at t_{max} ranging from 66% to 95%, although increased inhibition was not dependent on dose at doses > 300 mg, and gradually decreased over 24 h to 26-79% inhibition (27).

SAFETY

All data so far conclude that the DPP IV-specific inhibitor dutogliptin can be used safely in the management of type 2 diabetes as either monotherapy or in combination with available treatments for type 2 diabetes. The benefits of dutogliptin over current therapies include being unlikely to cause hypoglycemia due to the fact that for its substrate to be present there must be elevated blood glucose levels, for example, following feeding (28). In addition, dutogliptin is effective when taken orally and does not cause weight gain. Perhaps most importantly is the selective nature of dutogliptin in specifically targeting DPP IV itself rather than DPP 8 or DPP IX, inhibition of which has unwanted detrimental side effects (22).

CLINICAL STUDIES

Dutogliptin has been advanced to late-phase clinical trials and a number of clinical evaluations assessing its use in combination with existing treatments for type 2 diabetes or as monotherapy are under way or recruiting. A randomized, double-blind, placebo-controlled, multicenter investigation of the ability of dutogliptin to improve postprandial blood glucose levels in patients with type 2 diabetes was carried out by Phenomix (29, 30). The primary efficacy endpoint measure was the assessment of AUC for postprandial blood glucose over a 28-day period. The study enrolled 174 patients, with a mean age of 52 years, a mean BMI of 33 kg/m^2 and a mean baseline HbA_{1c} of 8.7%. Subjects received either placebo control or dutogliptin (100, 200 or 400 mg). Ninety-three percent of the patients were receiving metformin treatment and 7% were receiving both metformin and glitazone. The postprandial blood glucose $AUC_{0\text{-}2h}$ was significantly reduced in all treatment groups compared to placebo by approximately 20%, with the greatest decrease noted in the 100-mg dose group (–2.08 ± 0.51 mmol/L x h; $P < 0.005$). In addition, postprandial circulating GLP-1 $AUC_{0\text{-}2h}$ was significantly increased in all treatment groups compared to placebo, concomitant with a dose-dependent inhibition of DPP IV levels at 24 h of 50%, 80% and 90%, respectively, for 100, 200 and 400 mg. At day 28 when compared to day 1 all treatment groups receiving dutogliptin showed improved mean HbA_{1c} levels, elevated levels of circulating GLP-1 and dose-dependent ex vivo inhibition of DPP IV (53%, 73% and 78%, respectively, for 100, 200 and 400 mg). The study concluded that there were no serious AEs associated with dutogliptin treatment when used in patients receiving metformin or metformin in combination with glitazone, and treatment positively improved postprandial blood glucose regulation (30, 31).

Extension of the number of participants included in this study to 400 patients receiving dutogliptin 200 or 400 mg/day further supported the use of dutogliptin in the management of type 2 diabetes. In this extension, decreases in HbA_{1c} levels of –0.35% ($P < 0.006$) and –0.52% ($P = 0.001$), respectively, were seen for the 200- and 400-mg groups. In both dose cohorts the percentage of patients reaching HbA_{1c} levels indicative of successful treatment was 27%, 21% and 12%, respectively, for the high dose, the low dose and placebo controls. In addition, fasting plasma glucose was significantly reduced in treatment groups compared to control: –0.88 mmol/L ($P = 0.003$) and –1.00 mmol/L ($P < 0.001$), respectively, for doses of 200 and 400 mg. The postprandial plasma glucose $AUC_{0\text{-}2h}$ was significantly reduced by treatment to –1.63 mmol/L/h ($P = 0.032$) and –2.58 mmol/L/h ($P < 0.001$), respectively, for the 200- and 400-mg groups. Moreover, ex vivo inhibition of DPP IV at the 12-week examination point was 70% and 80%, respectively, for the 200- and 400-mg groups. In agreement with the prior studies, no significant AEs were attributed to the treatment (28).

A randomized, double-blind, placebo-controlled, multicenter phase III study to evaluate the safety and efficacy of dutogliptin as monotherapy for type 2 diabetes was carried out by Phenomix in collaboration with Forest Laboratories; the study began in June 2008 and was completed in April 2010 (32). The primary outcome measure of the study was the analysis of changes in glycated HbA_{1c} levels over 176 days. The study enrolled 480 patients with type 2 diabetes (age range: 18-75 years) who received dutogliptin (200 and 400 mg orally) or a placebo control. The results of this study have yet to be reported.

An open-label, multicenter trial phase II is currently under way to investigate the long-term safety of dutogliptin in treating type 2 diabetes (33). The trial began in April 2007 and is being conducted by Phenomix as an extension to the previously described protocol PHX1149-PROT202 (29). Primary outcome measures will include safety, assessment of vital signs and recording of AEs at 104 and 208 weeks. Secondary outcome measures will include determination of changes in HbA_{1c} levels and fasting plasma glucose at 104 weeks as an indicator of successful management of type 2 diabetes. To date, 339 patients have been enrolled and receive a daily oral dose of dutogliptin of 400 mg. Inclusion criteria include prior enrollment in the previous protocol and exclude patients receiving insulin therapy.

There are currently four phase III trials investigating the use of dutogliptin in treating type 2 diabetes. The first investigation is enrolling

patients from a previous protocol by invitation (34). This is a multicenter, double-blind, active-controlled extension study to evaluate the tolerability and efficacy of dutogliptin in patients with type 2 diabetes who are receiving current treatment with pioglitazone alone or glimepiride alone or in combination with metformin. The study began in March 2010, enrolled 1,050 patients and will be completed in 2012. Primary outcome measures will assess safety and efficacy by monitoring AEs, vital signs and ECG at 52 weeks following a dosing regimen of dutogliptin of 400 mg/day orally or sitagliptin 100 mg/day orally as an active comparator. Secondary outcomes will assess changes in HbA_{1c} and fasting plasma glucose.

The other three phase III trials are in the active phase. The first is a randomized, double-blind, placebo-controlled, multicenter investigation to evaluate the safety and efficacy in type 2 diabetes patients with a background of metformin treatment (35). This trial commenced in March 2009 and reached primary completion in October 2010. The study enrolled 700 patients (aged 18-75 years) who received either 400 mg dutogliptin or a placebo control and were assessed at 26 weeks for changes in baseline HbA_{1c} as a primary outcome measure of efficacy. Secondary outcome measures will assess drug tolerance and alterations in fasting plasma glucose levels. The second, an extension of the previous trial, is a randomized, double-blind, active-controlled, multicenter study to assess the safety and efficacy of dutogliptin (400 mg) with sitagliptin (100 mg) as the active comparator (36). This study began in November 2009 and will run for 2 years, and has enrolled 650 patients who were receiving metformin treatment and who had completed the core precursor protocol PHX1149-PROT302 (35). The primary outcome measures of safety and tolerability will be assessed by examining vital signs, ECG and AEs at 52 weeks. Secondary outcome measures will include assessment of changes in circulating plasma HbA_{1c} levels and fasting plasma glucose levels. The final phase III trial under way is an open-label, multicenter, long-term extension study to assess the safety and efficacy in patients with type 2 diabetes who are not receiving any other form of treatment (37) and who have completed the core precursor protocol PHX1149-PROT301 (32). The study began in March 2009, has enrolled 450 patients receiving dutogliptin (400 mg/day orally) and will run for 2 years. The primary outcome of the study is to assess long-term safety and efficacy of treatment, and secondary outcomes will examine changes in fasting plasma glucose and HbA_{1c} levels. The data from these three phase III studies have not yet been disclosed.

Finally there are two phase III trials in the recruitment stage. Both are randomized, double-blind, placebo-controlled, multicenter studies to evaluate the safety and efficacy of dutogliptin in patients with type 2 diabetes who are also being treated with glimepiride, with or without metformin (38) or pioglitazone (39). The primary outcome measures of both studies will be the assessment of changes in circulating HbA_{1c}, while the secondary outcome measures will monitor fasting plasma glucose levels.

SOURCES

Phenomix Corp. (US); licensed to Chiesi Farmaceutici (IT) for Europe and other regions.

DISCLOSURES

The author states no conflicts of interest.

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