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Novel Serine Protease Dipeptidyl Peptidase IV Inhibitor: Alogliptin

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Abstract: Alogliptin (codenamed **SYR-322**) is a recently approved anti-diabetic drug in Japan, which has been under clinical development phase III in USA and Europe. Alogliptin has been developed by Takeda under the brand name "Nesina". Alogliptin is a highly selective (> 10,000-time selectivity, potent, reversible and durable serine protease dipeptidyl peptidase IV enzyme is compared to DPP-8 and DPP-9) inhibitor, which has been developed as an alternative second-line to metformin in place of a sulphonylurea. Alogliptin has been observed to increase and prolong the action of incretin hormone by inhibiting the DPP-IV enzyme activity. Alogliptin has been observed to well absorb and show low plasma protein binding, which displays slow-binding properties to DPP-IV enzyme. The X-ray crystallography studies have been revealed that Alogliptin binds to DPP-IV active site by non-covalently and provides sustained reduction of plasma DPP-IV activity as well as lowering of blood glucose, in drug-naive patients with T2DM and inadequate glycemic control, once daily oral dosing regimen with varying levels of doses ranging from 25-800 mg. Alogliptin is approved as monotherapy and in combination with alpha-glucosidase & thiazolidinediones. The 26 week clinical study of Alogliptin revealed that Alogliptin doesn't increase the weight and well tolerated. In the present review, we have tried to cover biology of DPP-IV, molecular chemistry, chemical characterization, crystal polymorphic information, interaction studies, commercial synthesis, current patent status, adverse effects and clinical status of Alogliptin giving emphasis on the medicinal chemistry aspect.

Keywords: Alogliptin, Approval, Diabetes Type-II, Dipeptidyl Peptidase-IV, DDP-IV, DPP-IV Inhibitor**,** Emerging Target, GIP, Gliptins, GLP-1, Glucagon-like peptide, Incretin, NESINA, Non-Insulin-Dependent Diabetes Mellitus (NIDDM), SYR-322, Takeda.

INTRODUCTION

Diabetes mellitus is a complex metabolic syndrome, which is a major human health concern all over the world. It is estimated to that diabetes mellitus will affect approximate 300 million people by the year 2025 [1]. The prevalence of diabetes mellitus is increasing worldwide from estimated 2.8% in 2000 to 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [2]. The prevalence of T2DM Mellitus (T2DM) has reached epidemic proportions and continues to rise [3]. It causes a number of negative complications like retinopathy, neuropathy and peripheral vascular insufficiencies [4]. T2DM is a disorder of blood-glucose control owing to multiple metabolic abnormalities, including insufficient insulin secretion, impaired response of liver and peripheral tissues to insulin (insulin resistance), progressive loss of beta cell function, deregulation of glucagon secretion and disturbed incretin hormone physiology [5]. In T2DM, hyperglycemia is the key determinant of microvascular complications and the evidence that improving glycemic control lowers the risk of microvascular complications is unequivocal. Hyperglycemia also contributes to macrovascular complications [6, 7]. T2DM is a progressive disease characterized by insulin resistance and β-cell dysfunction, which includes other conditions, e.g. chronic hyperglycemia and subsequent augmentation of reactive oxygen species (ROS) that deteriorates β -cell function and increase's insulin resistance, which ultimately leads to the aggravation of T2DM [8].

Current therapy of T2DM involves the use of metformin, sulfonylureas, thiazolidinediones and insulin. There are a few emerging classes, which targets the incretin now they have been come into clinical use, e.g. the GLP-1 receptor agonists and dipeptidyl peptidase-IV (DPP-IV) inhibitors [9].

With an increasing number of newly diagnosed patients with T2DM worldwide, it is important to establish therapeutic strategies for such patients. Treatment often begins with life-style modifications (diet/exercise), which is regarded as the initial therapeutic option in the ADA/EASD consensus statement. However, many patients require or desire pharmacotherapy from the beginning. Currently, metformin considered as the first drug of choice in the treatment of T2DM, although other drugs could be potential candidates as well [10].

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Recent algorithms developed by the ADA/EASD have recommended the use of GLP-1 receptor agonists (monotherapy or combination therapy) on the basis of their effective glycemic efficacy, low frequency of hypoglycemic events, body weight loss, and overall safety profiles. On the contrary, due to their limited glucose lowering efficacy and lack of long-term safety profile, DPP-IV inhibitors are not actively considered a well-validated therapeutic option by these algorithms. At the present time, use of DPP-IV inhibitors as adds on to other drugs in more advanced diabetic subjects who require insulin is more common in actual clinical practice. However, it is no doubt that they have gained an important position in the actual clinical practice in the past several years [10].

DPP-IV inhibitors represent an innovative approach to treat NIDDM with a unique mechanism of action compared to other marketed oral hypoglycemic agents. DPP-IV inhibitors have been observed to bind with DPP-IV enzyme, consequently, inhibiting the breakdown of the incretin hormones and increasing GLP-1 and glucose-dependent insulinotropic peptide (GIP). GLP-1 and GIP are the naturally-occurring hormones, which are released by the gut after meals and target the pancreas by increasing glucose-dependent insulin secretion and suppressing glucagon secretion. DPP-IV inhibitors have been observed to increase the GLP-1 plasma concentration within the physiological range in contrast to injectable GLP-1 mimetic, which has supra-physiological plasma levels and has been associated with an increasing gastrointestinal side-effect rate, such as nausea and vomiting [3].

There are several gliptins available in the market and under advanced clinical trials including KRP-104, (ActivX, Kyorin, Phase II) Vildagliptin (Novartis Launched – 2007), Saxagliptin (Bristol- Myers Squibb Company, Launched – 2009), Sitagliptin phosphate monohydrate (Merck & Co, Banyu Ono, Launched - 2008), Teneligliptin (Mitsubishi Tanabe Pharma) Phase III, Linagliptin (Boehringer Ingelheim, Launched - 2011), KRP-104 (Kyorin, Phase II), Melogliptin (Glenmark Pharmaceuticals, Phase II), SK-0403 (Kowa, Sanwa, Phase III), ARI-2243 (Arisaph, Phase I), ALS-2-0426 (Amgen, Phase II), DB-160 (DARA BioSciences, Preclinical), DA-1229 (Dong-A, Phase II), Gemigliptin (LG Life Sciences, Phase III) and DSP-7238 (Dainippon Sumitomo Pharma, Phase I) [11].

Alogliptin was discovered by the Takeda Pharmaceutical Company. During the development, it was found that the quinazolinone based structure would have the necessary groups to interact with the active site on the DPP-IV complex. Quinazolinone based compounds interacted effectively with the DPP-IV complex.

The discovery of Alogliptin started from the fluorinated derivative, which showed improved metabolic stability and excellent inhibition of the DPP-IV enzyme. However, it was also found that it inhibits to CYP 450 3A4 and blocks the hERG channel. The solution to this problem was to replace the quinazolinone with other heterocyclics, but the quinazolinone could be replaced without any loss of DPP-IV inhibition. The metabolic instability was major problem with quinazolinone nucleus.

The solution to this problem was sorted by replacing the quinazolinone with a pyrimidinedione. Pyrimidinedione nucleus gives better metabolic stability as well as increased potency, and selectivity to DPP-IV enzyme. The quinazoline based compounds showed potent inhibition and excellent selectivity over related protease, DPP-8. However, short metabolic half-life due to oxidation of the ring phenyl group was problematic.

Alogliptin is an orally bioavailable quinazolinone based non-covalent inhibitor of DPP-IV. Alogliptin (code named SYR-322) is a new approved anti-diabetic drug, which is developed by Takeda under the brand name "Nesina, Tablets 25mg, 12.5mg & 6.25mg. Alogliptin is a potent, selective inhibitor of the serine protease dipeptidyl peptidase IV (DPP-IV). It is also known as SYR-322, generic name being Alogliptin benzoate. New Drug Application (NDA) of Alogliptin (Nesina®) is filed as a highly selective DPP-IV inhibitor for the treatment of T2DM. Alogliptin is approved in Japan for treatment of T2DM [12]. Alogliptin has been launched in Japan in 2010 as monotherapy and in combination with the alpha-glucosidase inhibitors for once daily treatment of T2DM [12, 13].

Biology of DPP-IV

DPP-IV enzyme is a non-classical, sequence-specific serine protease that catalyzes the cleavage of dipeptides from the N-terminus of proteins [15, 16] modulates the biological activity of specific circulating peptide hormones, chemokines, cytokines and neuropeptides by specifically cleaving two nitrogen terminal amino acid protein [17]. DPP-IV enzyme is known under depending upon location such as, CD26, Adenosine Deaminase Complexing Protein 2 (ADCP2), T-cell activation TP103 antigen. DPP-IV is imbedded on the epithelial brush boarderembedded membrane of the intestinal tract lining [17]. It is encoded by the DPP-IV gene, which is responsible for the initial rapid degradation of glucagon like peptide 1 (GLP 1) and glucglucagon-like insulinotropic polypeptide (GIP). DPP-IV inhibitors are a class of oral hypoglycemics that work by affecting the action of natural hormones in the body, formerly known as incretins, e.g GLP-1 and GIP [18]. The incretins play an important role in modulating islet cell function, gastric emptying and satiety [19]. DPP-IV is also responsible for the initial rapid degradation of both GLP 1 and GIP. Concentrations of the incretin hormones, e.g. GLP 1 and GIP are dependent to meals, which released into the blood stream from the small intestine in response. Incretins are rapidly degraded by the DPP-IV enzyme by cleaving the active peptide at the position 2 alanine (N-terminal) resulting in inactive peptide [20]. DPP-IV is widely expressed in human tissues including the brain, lungs, kidneys, adrenals, pancreas, intestine, and lymphocytes. DPP-IV enzyme affects the human body beyond its proteolytic action, like T-cell proliferation. In addition, many neuropeptides, growth factors, cytokines, and chemokines have been identified as potential DPP-IV substrates. The main role of DPP-IV enzyme is to cleave the N-terminal 2 amino acids of active GLP-1 to give the inactive GLP-1 amide. Degradation of GLP-1 leads to decrease in insulin secretion and biosynthesis. DPP-IV inhibitors are oral hypoglycaemic agents that result in around a four-fold increase in plasma GLP-1 levels. Due to the glucose-dependent

effects of GLP-1, DPP-IV inhibitors have also been associated with low risk of hypoglycemia [21, 22].

DPP-IV enzyme interacts with the diverse range of ligands selected from the natural ligands, e.g. Glucagon-like peptides-1 & 2, Glucose–dependent insulinotropic peptide, Neuropeptide Y, Substance P, Peptide YY, IGF-1, Prolactin, hCGα, Growth Hormone Releasing Factor, LHα, Thyrotropinα, Enkephalins, Vasostatin, Eotaxin, Interferon-γ inducible protein, IFN-inducible T-cell alpha-chemoattractant, Procalcitonin15, Macrophage-derived chemokine, Monokine induced by Interferon-γ [3].

DPP-IV enzyme involved in the regulation of several important physiological processes, e.g. Immune system, Inflamation, CNS, Endocrine functions, Bone marrow mobilization, Cancer growth, Cell adhesion, Glucose hemostasis, Sepsis/severe infection [3].

DPP-IV is also known as CD26, a cell-surface marker for T-cell activation that has a co stimulatory role in T-cell activation. Several lines of evidence indicate that its DPP-IV enzyme activity is not involved in CD26-mediated T-cell activation and proliferation. The most-recent study has shown that T-cell-dependent antibody responses, and cytotoxic T-cell responses are not affected when DPP-IV is selectively inhibited in mice [23].

Glucagon-like peptide-1 (GLP-1) is a member of the incretin family of neuroendocrine peptide hormones secreted from the L-cells of the intestine in response to food ingestion. GLP-1 has multiple metabolic effects that are attractive for an anti-diabetic agent. A key function of GLP-1 is to activate its receptor, GLP-1R, on pancreatic beta-cells to enhance glucose-dependent insulin secretion. Positive metabolic benefits of GLP-1 may include, but are not limited to, suppression of excessive glucagon production, decreased food intake, delayed gastric emptying and improvement of b-cell mass and function. The positive effects of GLP-1 on beta-cell mass and function offers the hope that GLP-1-based therapies may delay early stage disease progression. In addition, a GLP-1 agonist could be useful in combination therapies such as with insulin in patients with type 1 diabetes. Unfortunately, the rapid proteolysis of GLP-1 into an inactive metabolite limits its use as a therapeutic agent [24].

Validation of GLP-1R agonists as a therapeutic modality was achieved by Exendin-4 (Byetta® (Amylin Pharmaceuticals, Inc.)), is a medication for the treatment of T2DM. It belongs to the group of natural substrates incretin mimetics, which is administered as a subcutaneous injection (under the skin) of the abdomen, thigh, or arm, any time within the 60 minutes before the first and last meal of the day. A once-weekly injection has been approved under the name Bydureon. Dosing of Exendin-4 by subcutaneous administration lowers blood glucose and decreases HbA1c levels, which are important biomarker measurements for disease control. Therefore, an oral GLP-1 receptor agonist, e.g. oxyntomodulin and exendin-4, should provide glycemic control while offering the convenience of oral dosing. Further, because peptides, such as GLP-1, may lack sufficient oral bioavailability for consideration as oral drug agents, small-molecule modulators of GLP-1R with oral bioavailability are highly desired [24].

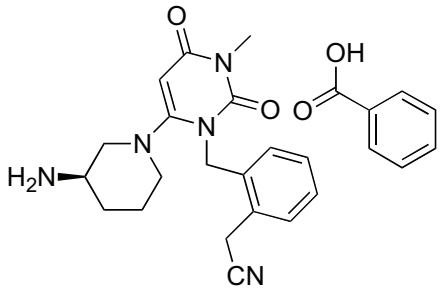


Fig. (1). Chemical structure of Alogliptin.

CHEMISTRY

Chemically Alogliptin is 2-[[6-[(3R)-3-amino-1-piperidinyl]-3,4-dihydro-3-methyl-2,4-dioxo-1(2H)-pyrimidinyl]methyl]-benzonitrile. CAS number: 850649-62-6**,** 850649-61-5 (free base); Molecular Formula: $C_7H_6O_2C_{18}H_{21}N_5O_2$; Molecular weight: 461.52; Generic Name Alogliptin Benzoate [25].

Patent Status

Product Patent

US Pat. No. 7807689; assigned to Takeda**;** was filed on March 15, 2005; prior published as US20050261271A1 & International Patent Application as WO05095381A1; Family equivalents EP1586571B1; JP2005263780; Compound Patent of Alogliptin. Claim 1, claims the Alogliptin basic structure, which covers the stereoisomers or pharmaceutically acceptable salts thereof [26].

Polymorphic Patent Application

US Pat. Publication No. 20070066635A1 continuation patent application US Pat. Publication No. 2009306379 (A1); assigned to Takeda Pharmaceutical; was filed on Sep 13, 2006; prior International Patent Application as WO2007035372 (A2); family equivalents EP1934198 (A2); JP2009514798 (T); claims the composition of Alogliptin polymorphs Form-A and amorphous Form 1, wherein novel polymorphic Form A characterized by XRD, IR, Raman and DSC [27].

Process Patents

US Pat. Publication No. 2009275750 A1; prior published as International Patent Application as WO2007035629 (A2); assigned to Takeda Pharmaceutical; was filed on Sep 15, 2006; family equivalent EP1924567 (A2); claims the process of preparation of markush pyrimidinedione derivatives, which generically covers the Alogliptin compound [26-28].

PHYSICO-CHEMICAL PROPERTIES

Alogliptin is crystalline and amorphous in nature as far as the polymorph is concerned Alogliptin in two polymorphic forms is reported in art, Form A and amorphous Form-I. Amorphous *Form-1* may be prepared by different methods like: by rotoevaporation from methanol; fast evaporation

from water; lyophilization from water; crystallization from ethyl acetate and hexanes; and crystallization from isopropyl acetate and hexanes which is characterized by X-ray powder diffraction pattern (XRD), IR spectrum, FT-Raman peak, differential scanning calorimetry (cyclic DSC) and thermogravimetric analysis (TGA) [29, 30].

IR Data of Amorphous Form-I

Absorption peaks at 809, 833, 868, 948, 1024, 1068, 1084, 1119, 1134, 1172, 1228, 1286, 1375, 1440, 1541, 1599, 1652, 1703, 2136, 2225, 2571, 2861, 2949 and 3062 cm^{-1} ; with an IR spectrum comprising unique FT-IR peak positions (peaks that show no other peaks within ±4 cm^{-1} to make up a unique set) at 809, 868, 1119, 1599 and 1703 cm^{-1}. *X-ray Powder Diffraction (XRD) of* amorphous *Form-I:* shows a broad halo with no specific peaks present. *FT-Raman peak position* at 805, 834, 904, 1002, 1024, 1045, 1134, 1168, 1205, 1280, 1386, 1443, 1578, 1600, 1654, 1703, 2225, 2864, 2958 and 3065 cm^{-1} ; with unique FT-Raman peak positions (peaks that show no other peaks within ±4 cm^{-1}) at 805, 1280 and 1703 cm^{-1}. *DSC:* spectrum having a Tg=70° C. (onset), exotherm at 132° C. (maxima), and an endotherm at 183° C. (onset temperature). Thermo gravimetric Analysis (TGA) analysis: *TGA* data showing a 4% weight loss from 25-151° C [29, 30].

Polymorphic crystalline Form A may be prepared by different method e.g. by crystallization from any of the following solvent systems (i) acetone, acetonitrile; butanol, dimethylsulfoxide; dioxane; ethanol; ethanol and isopropyl alcohol; (viii) ethanol and water; ethyl acetate; heptane; isopropanol; isopropyl acetate; methanol; methyl ethyl ketone; methyl isobutyl ketone; 2,2,2-trifluoroethanol; tetrahydrofuran; toluene; water; ethanol and heptane. *Polymorphic crystalline Form A shows following* XRD 2θ peaks

Peak Position (2θ)	I/I_O
9.44	56
10.84	28
17.82	50
18.75	100
25.87	16
28.52	25

IR spectrum of crystalline Form A shows absorption peaks at 830, 876, 910, 950, 987, 1004, 1026, 1063, 1094, 1135, 1173, 1212, 1231, 1284, 1316, 1334, 1365, 1384, 1447, 1458, 1474, 1532, 1592, 1613, 1697, 2082, 2230, 2540, 2596, 2743, 2860, 2958, 2979 and 3085 cm^{-1} ; with an IR spectrum comprising unique FT-IR peak positions (peaks that show no other peak within ±4 cm^{-1} to make up a unique set) at 1212, 1365, 1447, 1613 and 1697 cm^{-1} . *FT-Raman of crystalline Form A shows peak* at positions 825, 881, 910, 918, 987, 1003, 1027, 1039, 1065, 1084, 1103, 1135, 1157, 1167, 1172, 1184, 1206, 1235, 1288, 1337, 1365, 1385, 1417, 1446, 1461, 1474, 1557, 1577, 1597, 1624 1652, 1689, 2230, 2860, 2883, 2957, 2970, 2983, 3026, 3053 and 3070 cm^{-1}; with unique FT-Raman peak positions (peaks that show no other peaks within ±4 cm^{-1} to make up a unique set) at 1065, 1103, 1235, 1288, 1337, 1365, 1624, 1689, 2883, 2983 and 3026 cm^{-1}. *DSC of crystalline Form A:* having an endotherm range of about 173° C. to about 195° C., optionally an endotherm range of about 180° C. to about 190° C., and optionally an endotherm at 186° C. *TGA*: data showing a 0.2% weight loss from 26-159° C [29, 30].

MECHANISM

Glucagon-like peptide-1 (GLP-1 (7-36 amide or 7-37)), a 30-amino acid peptide hormone, is secreted by intestinal L-cells in response to meal ingestion and stimulates insulin secretion from β-cells while inhibiting hepatic glucose production. Furthermore, GLP-1 has been shown in mammals to stimulate the insulin biosynthesis, inhibit glucagon secretion, slow gastric emptying, reduce appetite, and stimulate the regeneration and differentiation of islet β – cells [31]. Continuous infusion of GLP-1 to patients with T2D results in significant reduction of blood glucose and hemoglobin A1c levels [28]. However, active GLP-1 is rapidly converted to inactive GLP-1 (9-36 amide or 9-37) by the serine protease dipeptidyl peptidase IV (DPP-IVa), thus limiting its therapeutic practicality. Inhibition of DPP-IV increases the levels of endogenous intact GLP-1 [31].

***In Vitro* Studies**

Alogliptin has been shown to be 10, 000-fold more selective for DPP-IV over other closely related proteins. Alogliptin blocks the degradation of GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide), which is formerly known as incretin. Incretins are normally released in the digestive tract in response to food and mediate glucose-dependent insulin secretion. GLP-1 also suppresses pancreatic glucagon secretion and subsequent liver glucose production, slows gastric motility and elicits satiety, a feeling of fullness. In T2DM, GLP-1 levels are decreased and the insulinotropic response to GIP is reduced, contributing to high blood sugar. DPP-IV inhibitors have displayed a weight-neutral profile along with a risk of low blood sugar similar to placebo due to their glucose-dependent mechanism of action [31]. Alogliptin is a highly selective (> 10,000-time selectivity for DPP-IV compared with DPP-8 and DPP-9) inhibitor. The DPP-IV activity is inhibited greater than 80% at 24 hours after dosing on day 14 across all doses, with enzyme inhibition sustained up to 168 hours after administration.

COMPUTATIONAL STUDIES

DPP-IV is a non-classical serine aminodipeptidase that removes Xaa-Pro dipeptides from the amino terminus (N-terminus) of polypeptides and proteins. DPP-IV dependent slow release of dipeptides of the type X-Gly or X-Ser has also been reported for some naturally-occurring peptides. Alogliptin is a non-covalent serine protease dipeptidyl peptidase IV inhibitor, which provides sustained reduction of activity and a lowering of blood glucose in animal models of diabetes. Structure-based drug design hypothesized SAR of quinazolinone scaffold with the active site residues of DPP-IV is shown in Figs. (**2**, **3** and **4**) [13].

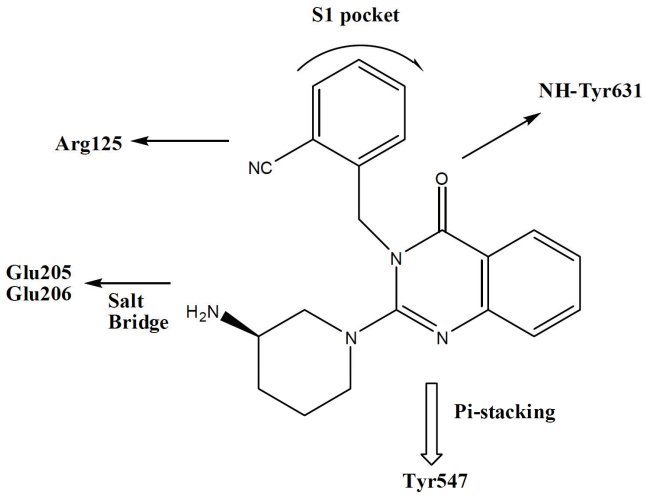


Fig. (2). Interaction of Quinazolinone scaffold with the active site residues of DPP-IV.

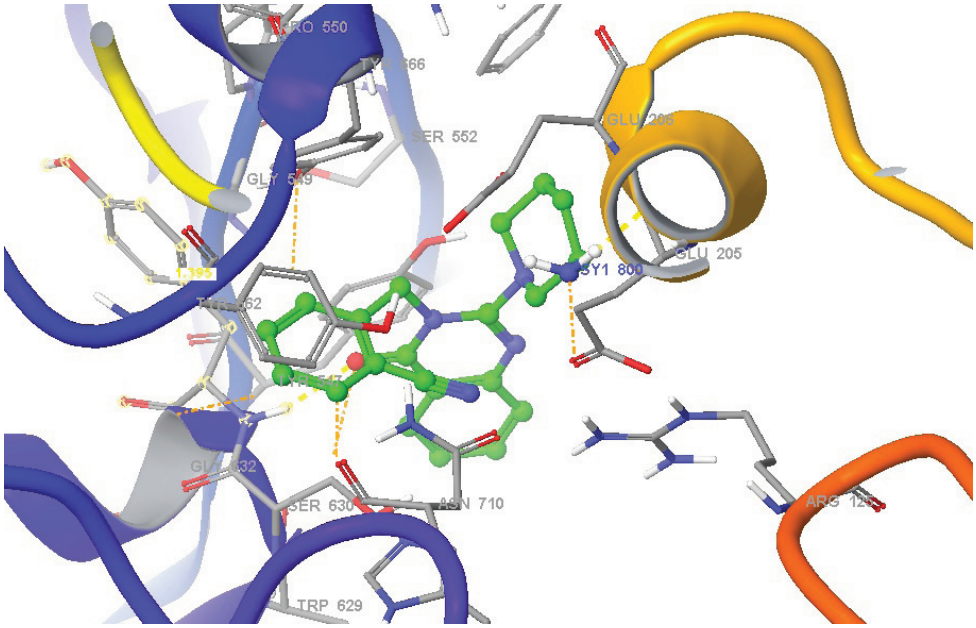


Fig. (3). Shows the interaction observation of quinazolinone scaffold with DPP-IV enzyme receptor [13,33].

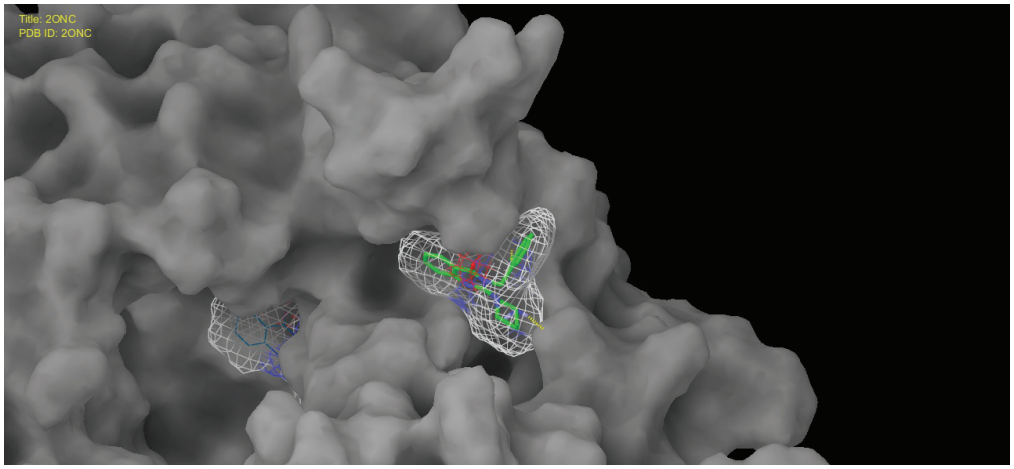


Fig. (4). DPP-IV active site surface [13].

Placing the aminopiperidine motif at C-2 predicted to provide a salt bridge to E205/E206 while a cyanobenzyl group at N-3 expected to effectively fill the S1 pocket (formed by V656, Y631, Y662, W659, Y666, and V711) and interact with Arg125. The carbonyl at C-4 anticipated to provide an important hydrogen bond to the backbone NH of Tyr631, and the bicyclic heterocycle predicted to ð-stack with Tyr547. In addition, since the quinazolinone scaffold is well represented in bioactive natural products and drugs, that it would impart favorable physical properties to the inhibitors [13].

Model of DPP-IV as depicted at Figs. (**4** and **5**), demonstrates that DPP-IV possess two active pockets namely S1and S2. In general, the inhibitors of the DPP-IV occupy the S1–S2 pocket at the DPP-IV active site and make extensive hydrophobic, van der Waals, and hydrogen-bonding interactions with residues lining this pocket [32]. Binding pocket possess essential structural requirement, including the catalytic triad residues forming residue Ser630, Asp708 and His740. In addition, Tyr547 in the hydrolase domain is essential for catalytic activity and in the crystal structure appears to stabilize the tetrahedral oxyanion intermediate form of a substrate [33]. Two glutamate residues in the catalytic pocket, at Glu205 and Glu206 as depicted in Fig. (**3**), align the substrate peptide by forming salt bridges to its N-terminus, leaving room for only two amino acids before the peptide reaches the active serine residue, thus explaining its dipeptides-cleaving activity. Furthermore, in the substrate, second position only amino acids with smaller side chains such as proline, alanine and glycine can fit into the narrow hydrophobic pocket.

X-ray co-crystal structure of DPP-IV (PDP entry code DPP-IV 2ONC) was obtained from Protein Data Bank, the protein was prepared by using the protein preparation wizard by Glide 5.0, and geometry was optimized. Ligand was extracted from the docked protein, saved in .SDF format and protein saved in .PDB format. The pose view of key interaction as depicted in the Fig. (**5**) was obtained from the pose-view online web portal by downloading the ligand in .SDF format and protein in PDB format [33, 34].

The crystal structure of DPP-IV demonstrates the substrate specificity of DPP-IV and the mutation data showing that Glu205 and Glu206 are essential for catalysis. An intriguing aspect of DPP-IV biochemistry is too dependent of peptidase activity upon homodimerization. Dimerization requires the hydrolase domain and a protrusion from the fourth blade of the β-propeller. A single amino acid point mutation near the C-terminus, His750→Glu, is sufficient to prevent dimerization [35]. Two glutamate residues (Glu205 and Glu206) in the ß propeller domain are highly conserved across the DPP family and are essential for its enzymatic activity [36]. The interaction with Glu205 is thought to be crucial interactions for Alogliptin, which formed two hydrogen bonds between the H of aminopiperdine and the carbonyl group of Glu205.

The C-terminal loop of DPP-IV highly conserved among prolyl dipeptidases, as essential for dimer formation and optimal catalysis. The conserved residue His750 on the loop contributes significantly for dimer stability. The quaternary structures of the wild type, H750A, and H750E mutant enzymes determined by several independent methods, including chemical crosslinking, gel electrophoresis, size exclusion chromatography, and analytical ultracentrifugation DPP-IV exists as dimers both in the intact cell and *in vitro* after purification from human semen or insect cells. The H750A mutation results in a mixture of DPP-IV dimers and monomer. H750A dimer has the same kinetic constants as those of the wild type, whereas the H750A monomer has a 60-fold decrease in *k*cat. Replacement of His750 with a negatively charged Glu (H750E) results in nearly exclusive monomers with a 300-fold decrease in catalytic activity [37].

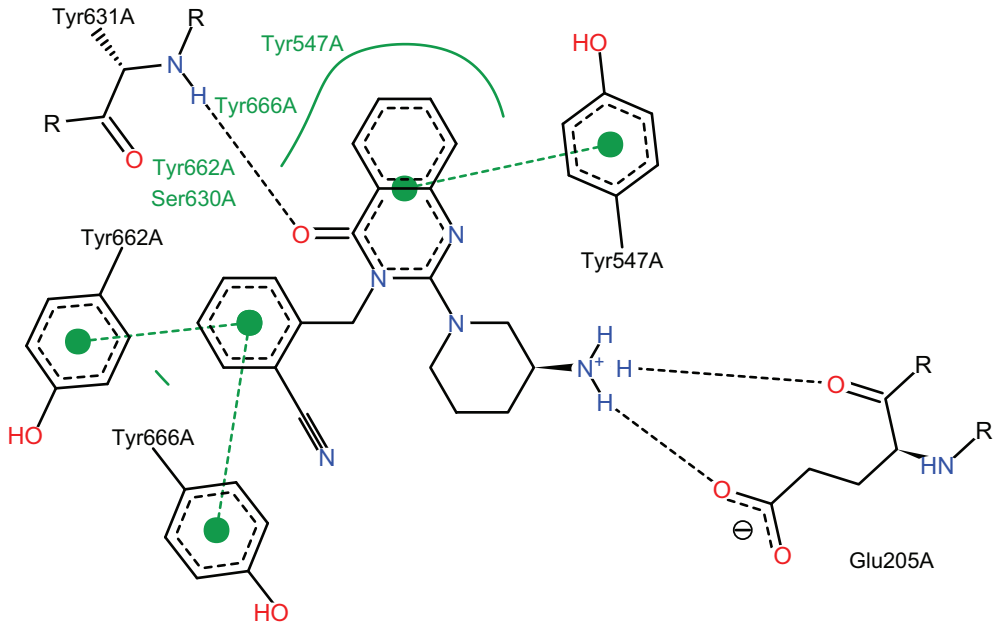


Fig. (5). Quinazolinone scaffold in the active site of DPP-IV with key interaction [13, 34].

COMMERCIAL PRODUCTION

Condensation of 6-chloro-1H-pyrimidine-2,4-dione (I) with an aryl halide of the compound formula (II) to produce a compound of the formula (III); Alkylating the formula (III) with a methyl halide under conditions sufficient to form a compound of the formula (IV); followed by condensing the result and product with a compound of the formula (V) to get Alogliptin base. The benzoic acid salt forms by treating with benzoic acid to form 2-[6-(3-amino-piperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-ylmethyl]-benzonitrile benzoate (Alogliptin) [26, 30].

INDICATION

Alogliptin has been indicated for T2DM in patients with inadequately hyperglycemia controlled by following treatments, treatment by diet and exercise only and treatment by the alpha-glucosidase inhibitors. Dosage and Usage: NESINA is orally administered to adults once daily as Alogliptin 25mg.

DOSE REGIMEN

Alogliptin is usually administered once daily and supportive of a once daily oral dosing regimen with varying levels of doses ranging from 25-800 mg. However, there is no dose-dependent suppression of DPP-IV activity. Alogliptin has been administered individually or as an add-on therapy to other drugs like Metformin, Glyburide and other diabetes medications [34, 38].

Gliptins

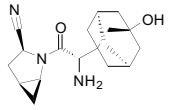
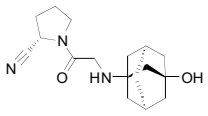
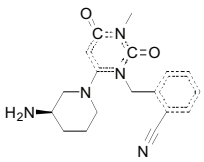
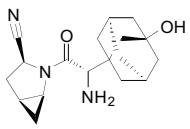
DPP-IV inhibition increases 2 to 4 fold in active GLP-1 levels in response to Alogliptin that is significant after meals [34, 39]. This is similar to GLP-1 values observed with sitagliptin treatment [34, 40]. Alogliptin is primarily excreted unchanged in the urine accounting for ~60% to 71% of the administered dose [34, 41]. However, a multiple-dose drug interaction study done with Alogliptin and metformin found no pharmacokinetic interaction [34, 42].

The comparative met-analysis study of sitagliptin and vildagliptin with placebo demonstrate in significant reduction of HbA1c values, –0.6% with sitagliptin (95% CI –0.8 to −0.4, P<0.00001) and –0.7% with vildagliptin (95% CI −0.9 to −0.6, P < 0.001).70 Combination therapy resulted in additional lowering of HbA1c with both agents, even though, it is proven that monotherapy with either DPP-IV inhibitor has inferiority in comparison to monotherapy with either metformin or sulfonylurea's [34, 43]. Saxagliptin is shows placebo-adjusted HbA1c reductions of −0.45% to −0.63% [34, 44, 45]. The improvements in HbA1c seen with Alogliptin appear to be in the same range as with the alternative DPP-IV inhibitors. The overview of selected DPP-IV inhibitors is presented in Table **1**.

PRECLINICAL STUDIES

Orally administered Alogliptin demonstrates effective antidiabetic activity in preclinical studies in mice, rats, dogs and monkeys and also provides better safety profile. Clinical studies demonstrate that Alogliptin can be safely co-administered with antidiabetic drugs such as pioglitazone,

Table 1. Overview of Selected DPP-IV Inhibitors [35,47,48]

Drug/Trade Name (Originator)	Chemical Structures	Dosage (mg/day)/ Route	Average A1C* Lowering	Elimination (%)		Half-life (hrs)	Dosing Frequency	Weight Effects
				Hepatic	Renal			
Sitagliptin Januvia (Merck)		100 / Oral	0.5%-0.8%	~13	~87	~12.4	q.d.	↔ ↑
Vildagliptin Galvus (Novartis)		100 / Oral	0.5%-0.8%	~15	~85	~2.1	q.d. or b.i.d.	↔ ↑
Alogliptin Nesina (Takeda Pharmaceutical)		25 / Oral	0.5%-0.8%	~40	~60	12.5-21.1	q.d.	↔ ↑
Saxagliptin Ongylza (Bristol Myres Squibb-Astra Zeneca)		2.5 or 5 / Oral	0.5%-0.8%	40-67	33-60	~2.8	q.d.	↔ ↑

*A1C- Glycosylated hemoglobin.

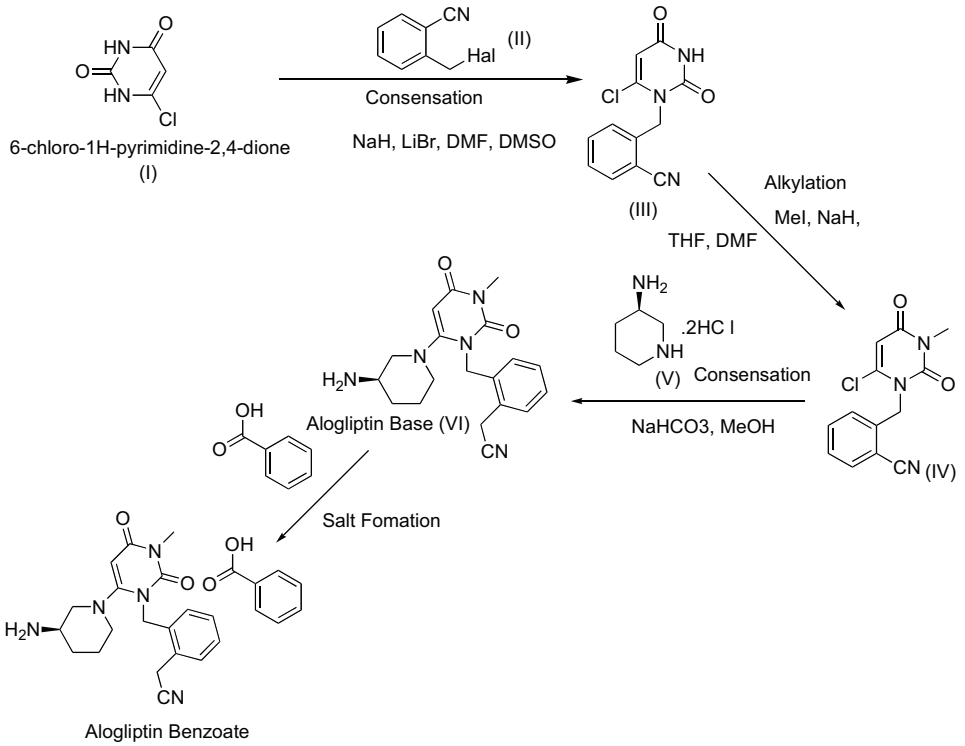


Fig. (6). Reaction Scheme.

glyburide, metformin and Warfarin without the need for dose adjustment. Alogliptin also demonstrated efficacy in reducing glucose and increasing insulin levels and proved to be well tolerated in healthy subjects and patients with T2DM [34, 41, 46]. Streptozotocin-induced diabetes rats, to which glibenclamide 10 mg/kg per day was given for 27 days and divided into four groups at 20 weeks of age. The four groups were placebo, glibenclamide 10 mg/kg/day, nateglinide 50 mg/kg/day, or Alogliptin 1 mg/kg/day prior to an oral glucose load (1 mg/kg) respectively. Alogliptin significantly increased the plasma insulin concentration at 10 minutes and decreased the glucose AUC from 0–120 minute glucose compared with rats receiving glibenclamide and nateglinide prior to the oral glucose load. In a separate group of diabetic rats, DPP-IV activity and plasma, GLP-1 levels (GLP-1 [7-36 amide] and GLP-1 [7-37 amide]) were inversely related to the dose of Alogliptin over the range 0.03–3.0 mg/kg [34, 46, 48].

CLINICAL TRIALS

Initial clinical trials were conducted to evaluate the pharmacokinetic (PK), pharmacodynamic (PD) and tolerability profiles and explore the efficacy of single-dose of Alogliptin in patients with T2D in 36 healthy men with randomized, double-blind, placebo-controlled, parallel-group study. (25, 50, 100, 200, 400, or 800 mg in a capsule formulation) [34, 46, 49]. In double-blind, multiple-dose study, 56 patients with T2DM were randomly assigned to receive once-daily Alogliptin 25, 100, 400, or 800 mg capsules or placebo for 14 days [39].

An open-label study evaluated the potential for Alogliptin–metformin interaction in 36 healthy subjects [39, 50]. Participants received, in randomized order, 6 days of Alogliptin 100 mg once daily, metformin 1000 mg BID, or both agents together. In a randomized, crossover, study performed in 30 healthy men and women, participants received, in randomized order, oral, once-daily Alogliptin 25 mg, pioglitazone 45 mg, or both agents in combination, each for 12 days. A nonrandomized, sequential study in 24 healthy men and women assessed the effects of Alogliptin on the pharmacokinetic properties of glyburide. Participants received a single 5-mg oral dose of glyburide alone and after 8 days of Alogliptin 25 mg once daily. In a study, 24 healthy subjects received, in randomized order, 10-day periods of Alogliptin 25 mg/d, digoxin 200 µg/d, or both drugs together, all administered orally. The pharmacokinetic properties were assessed in the presence and absence of the other drug and expressed as combination: monotherapy LS mean ratios. All of the 90% CIs were within the pre specified range for bioequivalence (0.80 –1.25) [39, 51].

In an open-label, single-dose study, 24 healthy men received, in randomized order, Alogliptin 25 mg alone or combined with cyclosporine 600 mg in crossover fashion [52]. A double-blind study enrolled 527 patients with HbA1c 7.0% to 10.0% who were receiving a stable metformin regimen (≥1500 mg/d). Patients were randomly assigned to receive Alogliptin 12.5 mg/d, 25 mg/d, or placebo added to metformin for 26 weeks. HbA1c was improved to a significantly greater extent with Alogliptin 12.5 mg (-0.6%) and 25 mg (-0.6%) than with placebo (-0.1%) and improvement in FPG was also significantly greater with Alogliptin 12.5 mg (-19 mg/dL) and 25 mg (-17 mg/dL) than with placebo (0 mg/dL). The incidences of hypoglycemia were ≤1% with each dose of Alogliptin [53].

Takeda has previously tested the efficacy and safety of Alogliptin in a Phase II study. Alogliptin was dosed once daily at 12.5 mg and 25 mg in combination with metformin in patients whose HbA1c levels were inadequately controlled on metformin alone. Alogliptin at both doses produced significant ($p < 0.001$) decreases from baseline in HbA1c greater than those observed with placebo. Differences between (Alogliptin vs. placebo) in fasting plasma glucose reached statistical significance ($p < 0.001$) as early as the first week and persisted for the duration of the study [53].

Overall, adverse events observed with Alogliptin were not substantially different from those observed with placebo. This includes low event rates for gastrointestinal side effects and hypoglycaemic episodes.

The results indicate that Alogliptin is an effective and safe treatment for T2DM, when added to metformin for patients not sufficiently controlled on metformin monotherapy [54].

In a randomized, double-blind study in 500 patients with inadequate glycemic control while receiving sulfonylurea monotherapy, treatment with Alogliptin 12.5 mg, Alogliptin 25 mg, or placebo was added for 26 weeks [55]. Reduction of HbA1c by Alogliptin 12.5 mg (-0.39%) and 25 mg (-0.53%) were significant compared with the change seen with placebo (-0.01%). Changes in FPG were -4.7 mg/dL with Alogliptin 12.5 mg, -8.4 mg/dL, Alogliptin 25 mg/dL, and -2.2 mg/dL with placebo. Alogliptin 12.5 and 25 mg were associated with HbA1c significant reductions from baseline of 0.56% and 0.59%, respectively, compared with 0.02% with placebo in a 26-week monotherapy study in 329 patients and significant HbA1c reductions of 0.66% and 0.80%, respectively, compared with 0.19% with placebo in a 26-week study of Alogliptin added to a regimen of TZD monotherapy or in combination with metformin or a sulfonylurea in 493 patients [53].

Alogliptin is approved in combination with thiazolidinediones (Pioglitazone) in Japan. Studies were conducted for 26 weeks. This 26-week, double-blind, parallel-group study randomized 655 patients with inadequately controlled T2DM to four arms: 25 mg Alogliptin (A25) q.d. monotherapy, 30 mg pioglitazone (P30) q.d. monotherapy, or 12.5 (A12.5) or 25 mg Alogliptin q.d. plus pioglitazone (P30) q.d. combination therapy. Primary efficacy was A1C change from baseline with the high-dose combination (A25 + P30) versus each monotherapy. Results of combination therapy with A25 + P30 resulted in greater reductions in A1C ($-1.7 \pm 0.1\%$ from an 8.8% mean baseline) vs. A25 ($-1.0 \pm 0.1\%$, $P < 0.001$) or P30 ($-1.2 \pm 0.1\%$, $P < 0.001$) and in fasting plasma glucose (-2.8 ± 0.2 mmol/l) vs. A25 (-1.4 ± 0.2 mmol/l, $P < 0.001$) or P30 (-2.1 ± 0.2 mmol/l, $P = 0.006$). The A25 + P30 safety profile was consistent with those of its component monotherapies [56].

Alogliptin has been studied as monotherapy and in combination with metformin, sulfonylurea, TZDs and insulin. Combination Alogliptin-Pioglitazone therapy improved beta cell function compared with Alogliptin alone [57, 58]. Alogliptin 12.5 mg and 25 mg plus combination provided significant improvements in A1C and FPG compared with placebo plus combination.

Patients with T2D between the ages of 18 and 75 years were assigned to receive a single oral dose of Alogliptin 25 mg, 100 mg or 400 mg or placebo (4:4:4:3 ratio) once daily for 14 days. The study assessed PK profiles, plasma DPP-IV inhibition, tolerability and efficacy end points, plasma glucose, HbA1c, C-peptide and fructosamine values. The results indicate that in these adult patients with T2D, Alogliptin inhibited plasma DPP-IV activity and significantly decreased plasma glucose levels. A once-daily dosing regimen was supported by the PK and PD profiles. Alogliptin was generally well-tolerated, with no dose-limiting toxicity and significantly improved glycemic control in these patients with T2D without raising the incidence of hypoglycemia [48].

Alogliptin was tested for efficacy and safety in elderly individuals (aged ≥65 years). The patients received 12.5 mg or 25 mg Alogliptin or placebo for 26 weeks. A pooled analysis was done on the elderly patients of six randomized, double-blind, placebo-controlled studies. Alogliptin was found to be effective and well-tolerated in the elderly patients. Improvement in HbA1c was similar to those seen in younger patients; risk of hypoglycemia was not increased; weight gain or other adverse events were apparent in elderly patients [56].

A pooled analysis was done on the 455 patients (mean baseline HbA1c = 8.0%) aged ≥65 years for 26 weeks, who received Alogliptin 12.5 or 25 mg/d (n = 175 for each group) or placebo (n = 105). The respective reductions from baseline HbA1c were 0.69% and 0.77% for Alogliptin (both, $P < 0.05$) and 0.18% for placebo. The incidences of hypoglycemia with Alogliptin 12.5 or 25 mg/d and placebos were 8.0%, 7.4%, and 10.5%, respectively; and the respective reductions in body weight were 0.03, 0.05, and 0.22 kg [56].

Takeda developed a combination of Alogliptin and metformin in a single tablet for the treatment of T2DM. The combination is presently in Phase III studies to test its safety and efficacy. The primary outcome measure will change from baseline HbA1c. For patients diagnosed with T2DM, metformin is the usual first-line therapy in addition to diet control and exercise. For patients with inadequate glycemic control with metformin or those who experience serious side effects of metformin, sulfonylurea is a popular choice as a second-line oral anti-diabetic treatment. Alogliptin slows the inactivation of incretin hormones, GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide), which play a major role in regulating blood-glucose levels and have the potential to improve pancreatic beta-cell function.

Alogliptin was tested in 329 drug-naïve patients with inadequately controlled T2D in a double-blind, placebo-controlled, multicenter study. Patients were randomized to once-daily treatment with 12.5 mg or 25 mg Alogliptin or placebo for 26 weeks. The primary efficacy end point was HbA(1c). Alogliptin was well-tolerated and significantly improved glycemic control in these patients with T2D without raising the incidence of hypoglycemia [59].

Takeda has previously tested the efficacy and safety of Alogliptin in a Phase II study. Alogliptin was dosed once daily at 12.5 mg and 25 mg in combination with metformin in patients whose HbA(1c) levels were inadequately controlled on metformin alone. Alogliptin at both doses produced significant ($p < 0.001$) decreases from baseline in HbA(1c) greater than those observed with placebo. The between-treatment differences (Alogliptin vs. placebo) in fasting plasma glucose reached statistical significance ($p < 0.001$) as early as the first week and persisted for the duration of the study as shown in Table **2** [31].

The study based on Alogliptin versus very low fat/calorie traditional Japanese diet (non-inferiority trial) as an initial therapy for newly diagnosed. Study design was the prospective, randomized, non-double-blind, controlled trial. The patients randomly received 12.5–25 mg/day Alogliptin ($n = 25$) or severe low calorie traditional Japanese diet ($n = 26$). The primary end point was the change of HbA1c at 3 months. Secondary end points included the changes of fasting blood glucose, insulin, homeostasis model assessment-R (HOMA-R), HOMA-B, body mass index (BMI), and lipid parameters.

Similar, significant reductions of HbA1c levels were observed in both groups (from 10.51 to 8.74% for Alogliptin and from 10.01 to 8.39% for traditional Japanese diet) without any clinically significant adverse events. In the Alogliptin group, some subjects (16%) had been mild hypoglycemic evens, which could be managed by taking glucose drinks by themselves. HOMA-B significantly increased in both groups with varying degrees, whereas HOMA-R significantly decreased only in the Japanese diet group.

Atherogenic lipids, such as, total cholesterol, non-high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels significantly decreased in both groups. There was no change in BMI the Alogliptin group, whereas it significantly decreased in the Japanese diet group.

Concerning its glycemic efficacy, Alogliptin is effective and non-inferior to traditional Japanese diet as an initial therapeutic option for newly diagnosed T2DM. However, regarding the reductions of body weight and insulin resistance, traditional Japanese diet is superior. Both Alogliptin and traditional Japanese diet have favorable effects on atherogenic lipid profiles. Alogliptin and traditional Japanese diet were similarly effective in reducing HbA1c or FBG levels [10].

Treatment with Alogliptin and Alogliptin /Pioglitazone produced significant reductions in postprandial triacylglycerol and triacylglycerol rich lipoproteins, contributing to an improved overall cardiometabolic risk profile in T2DM. The data support the concept that incretins not only modulate glucose metabolism but also influence chylomicron metabolism in intestinal cells. At week 16, Alogliptin (n=25) and Alogliptin / Pioglitazone (n=21) vs Pbo (n=24) produced similar significant reductions in total postprandial TG response (incremental AUC [iAUC]; $p<0.001$), as well as in chylomicron TG ($p<0.001$) and VLDL1 TG iAUCs ($p<0.001$ and p00.012, respectively) [10].

The study conducted by B. Eliasson *et al.* for funding provided by Takeda Global Research & Development observed that robust additive effects of Alogliptin/Pioglitazone treatment, as compared with Alogliptin alone, on HbA1c, FPG and HOMA-IR index, as data depicted in Table **3**.

DRUG INTERACTION

Alogliptin has not been associated with any significant drug-drug or drug food interaction. Alogliptin may be taken without regard to meals. Pioglitazone increased the AUC of Alogliptin by 10%, but this is considered to be of no clinical significance [60, 62]. In addition to metformin, drug interaction studies were done with other common antidiabetic agent's glyburide and pioglitazone [63, 64]. Studies with CYP inhibitors disclosed no significant interactions with fluconazole, ketoconazole and gemfibrozil [65]. Other interaction studies with warfarin, cyclosporine, ethinylestradiol and norethindrone, atorvastatin and digoxin were also reassuring [62, 67, 68]

ADVERSE REACTION

Skin Toxicity

Alogliptin studied incorporated a search for skin lesions, with a marginally higher rate than in the placebo, the major finding being pruritus [9]. Patients with renal and hepatic impairment: Alogliptin 50 mg administered to patients with renal impairment and did not cause any increase in adverse events [66]. It was given to 6 subjects in each group of mild, moderate, severe and end-stage renal disease, and 25% experienced at least one AE, but were judged to be mild and unrelated to drug. Alogliptin monotherapy had slightly adverse events related to the gastrointestinal system- abdominal pain, nausea, diarrhea, and vomiting. The most frequent adverse event with Alogliptin therapy in clinical trials was headache, dizziness, and constipation. Some patients have also reported skin reactions [60].

PHARMACOKINETICS

The pharmacokinetic and pharmacodynamic profiles of Alogliptin in healthy subjects were evaluated with single doses of 6.25 mg, 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, and 800 mg. Multiple-dose studies were done in subjects with T2DM and doses of 25 mg, 100 mg and 400 mg were given for 14 days. Alogliptin is rapidly absorbed after oral administration with median T-max ranging from 1 to two hours across all doses. Mean half-life was 12.4 to 21.4 hours across all doses [67].

CONCLUSION

Alogliptin raises postprandial levels of GLP-1 as well as showed excellent bioavailability, exhibiting a median T-max ranging from 1 to two hours and a mean half-life of 12.4 to 21.4 hours across all doses. When Alogliptin is given as monotherapy, mean hemoglobin A1c (HbA1c) reductions achieved were 0.5% to 0.6%. Combination therapy yielded similar reductions (−0.5% with metformin, −0.6% with glyburide, −0.8% with Pioglitazone and –0.6% with insulin). Administration of Alogliptin does not promote weight loss but has not resulted in weight gain. The agent is relatively well tolerated with few adverse effects, the major finding being a marginally higher rate of skin events, primarily pruritus.

Table 2. Changes in glycemic parameters in randomized, controlled Alogliptin clinical trials of dipeptidyl peptidase-4 inhibitors in patients with T2DM [47, 54, 56, 57, 61, 62]

N	WKs	Baseline HbA_{1C} (%)	Intervention	HbA	FPG (mg/dL	Weight (kg)	Hypoglycemia (%)	Severe Hypoglycemia (%)	
329	26	7.9	Placebo	0	+11	+0.2	1.6	0	Initial Phase
			Alogliptin 12.5 mg	−0.6	−10.3	–0.1	3	0	
			Alogliptin 25 mg	−0.6	−16.4	–0.2	1.5	0	
500	26	8.1	Placebo + glyburide	0	+2.2	–0.2	11.1	0	Initial Phase
			Alogliptin 12.5 mg + glyburide	−0.4	−4.7	+0.6	15.8	0	
			Alogliptin 25 mg + glyburide	−0.5	−8.4	+0.7	9.6	0	
493	26	8.0	Placebo + pioglitazone ± metformin/sulfonylurea	−0.2	−5.7	+1.0	5.2	0	Initial Phase
			Alogliptin 12.5 mg + pioglitazone ± metformin/sulfonylurea	−0.7	−19.7	+1.5	5.1	0	
			Alogliptin 25 mg + pioglitazone ± metformin/sulfonylurea	−0.8	−19.9	+1.1	7.0	0	
390	26	9.3	Placebo + insulin ± metformin	−0.1	5.8	0.6	24	0.5	Alogliptin was tested for efficacy and safety in elderly (65 or older) and younger patients with T2D.
			Alogliptin 12.5 mg + insulin ± metformin	−0.6	2.3	0.7	26.7	0	
			Alogliptin 25 mg + insulin ± metformin	−0.7	−11.7	0.6	27.1	0.25	
527	26	7.9	Placebo + metformin	−0.1	0	-0.4	2.9	0	Phase II
			Alogliptin 12.5 mg + metformin	−0.6	−19	-0.4	0.9	0	
			Alogliptin 25 mg + metformin	−0.6	−17	-0.7	0	0	

Table 3. Comparative Figure of Alogliptin/Pioglitazone VS Alogliptin Alone

SN	Characteristic	Placebo n=24	Alogliptin n=24	Alogliptin/Pioglitazone n=22
1	Diabetes duration (years)	5.5 (3.2)	6.4 (3.6)	5.0 (3.8)
2	HbA1c (%)	6.6 (0.7)	6.8 (0.8)	6.6 (0.6)
3	HbA1c (mmol/mol)	49 (8)	51 (9)	49 (7)
4	FPG (mmol/l)	8.9 (1.6)	9.3 (2.8)	8.5 (2.0)
5	Fasting plasma insulin (pmol/l)	126.4 (63.9)	116.0 (53.5)	116.0 (72.2)
6	HOMA-IR (%)	7.1 (3.5)	6.9 (3.6)	6.7 (5.4)
7	Metformin/other	OHA 23 (96)	22 (88)	21 (95)
8	Lipid-lowering agents	13 (54)	15 (60)	12 (55)

The above studies have been suggested that Alogliptin can play an important role in the treatment of T2DM mellitus. In elderly patients, in whom concerns about hypoglycemia is greatest and who cannot take either metformin or a thiazolidinedione, thus precluding sulfonylurea therapy, gliptins may be the agents of choice.

The interaction studies observed that two glutamate residues (Glu205 and Glu206) in the ß propeller domain are highly conserved across the DPP family and are essential for its enzymatic activity. The interactions with Glu205 are thought to be crucial interactions for Alogliptin, which formed two hydrogen bonds between the H of amino-piperidine and the carbonyl group of Glu205.

The clinical trials reviewed here suggest that gliptins have glucose-lowering efficacy similar to that of other oral anti-hyperglycemic therapies, with minimal risk of hypoglycemia, with few immediate adverse effects and without requiring dose-titration. These observations suggest that gliptins should be considered useful agents in mono-therapy and combination therapy with the metformin and thiazolidinediones or insulin for the treatment of T2DM mellitus.

In summary, Alogliptin has been found variably effective in reducing HbA, FPG and PPG levels in patients with T2DM patient due to their unique mechanisms of action. Alogliptin would be used alone; gliptins generally lowers HbA 1c 0.5% to 0.8%. An oral dose of Alogliptin, which is a non-covalent inhibitor, provides sustained reduction of plasma DPP-IV activity and a lowering of blood glucose in animal models of diabetes. Alogliptin generally possesses good safety profiles in addition to the existing anti-hyperglycemic therapy, which provides similar additional improvement in glycemic control and could prove to be a new alternative to the currently available medications in future due to low risk of hypoglycemia.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest by any means with respect to the instant manuscript.

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ABBREVIATIONS

Baseline HbAIC (%)	=	Mean Hemoglobin A1C
BMI	=	Body Mass Index
GIP	=	Glucose-Dependent Insulinotropic Polypeptide
GLP-1	=	Glucagon-Like Peptide-1
HbA1	=	Hemoglobin A1
FPG (mg/dL)	=	Fasting plasma glucose
NIDDM	=	Non-Insulin-Dependent Diabetes Mellitus

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