# DPP-4 Inhibitors: A New Therapeutic Class for the Treatment of Type 2 Diabetes

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Type 2 diabetes (T2D) is characterized by altered glucose homeostasis, including decreased insulin sensitivity of target tissues, a gradual decline in β-cell insulin production and secretion, and a progressive inability to suppress pancreatic α-cell glucagon secretion.[1] In the past, goals for therapy have focused primarily on insulin secretion, sensitization, and replacement. However, newer T2D medications utilize the incretin gut hormone pathway, a focus of scientific and clinical research for decades.[2] The so-called *insulin effect,* known today as the *incretin effect*[3]—ie, greater insulin secretion in response to nutrient ingestion—was identified in 1964 when Elrick et al[4] demonstrated that orally administered glucose produced a significant and sustained increase in plasma insulin, whereas intravenously administered glucose produced a smaller and transient insulin increase. This finding was paramount in bringing incretin-based therapies to clinical practice.

The 2 most well characterized incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (**Figure 1**). Currently, therapeutic agents, acting as either an incretin mimetic (via GLP-1 analogs) or to inhibit the breakdown of GLP-1 (via dipeptidyl peptidase-4 [DPP-4] inhibitors) are available for treatment.[2,3] Various DPP-4 inhibitors are in development, and 2 are approved by the US Food and Drug Administration (FDA): Sitagliptin and the recently approved DPP-4 inhibitor, saxagliptin, are indicated for use in a broad range of patients, including those who are drug naïve or who have inadequate glycemic control on another oral antidiabetic drug (OAD). Both agents are approved as monotherapy and as an add-on to current antihyperglycemic therapy (ie, metformin [MET], sulfonylurea [SU], thiazolidinedione [TZD]), and are also approved as initial combination therapy with MET.[5-7] Another DPP-4 inhibitor, alogliptin, failed to gain approval from the FDA, which indicated the need for additional data (Takeda Pharmaceutical Company Limited [takeda.com]) (**Table 1**).

**[SIDEBAR]**

## DIPEPTIDYL PEPTIDASE-4 INHIBITORS COMPLEMENT OTHER ORAL ANTIHYPERGLYCEMIC AGENTS

The current therapeutic options for treating type 2 diabetes (T2D) include drug classes that lower blood glucose levels by different mechanisms of action (**Table**) through various target organs.[1,2]

**Table. Drug classes that lower blood glucose levels**

| Agent(s) | Mechanism of Action |
|---|---|
| • Insulin<br>• Sulfonylureas<br>• Glinides | Insulin replacement/secretion |
| • Thiazolidinediones | Insulin sensitization |
| • Biguanides | Decrease of hepatic glucose output |
| • α-Glucosidase inhibitors | Delay of intestinal carbohydrate absorption |
| • DPP-4 inhibitors<br>• GLP-1 analogs | Incretin enhancement/replacement with subsequent effects on insulin secretion |

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

Glucagon-like peptide-1 (GLP-1) is known to enhance insulin release from the pancreatic β-cells and inhibit glucagon release through the α-cells in a glucose-dependent manner.[3] In the fasted state, circulating levels of GLP are low but rise within minutes of meal ingestion. GLP-1 is released from the L cells of the small intestine within minutes of food consumption; however, incretin hormones are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4).[3] By inhibiting DPP-4, the DPP-4 inhibitors enhance the half-life of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), thereby augmenting their levels.[1,4] Because the release of GLP-1 is glucose dependent, augmentation of GLP-1 by

DPP-4 inhibition minimizes the risk for hypoglycemia, which proves to be clinically important in managing T2D.

The majority of antidiabetic agents act primarily by lowering fasting plasma glucose (FPG) (eg, sulfonylureas), whereas others act primarily by lowering postprandial glucose (PPG).[5] DPP-4 inhibitors primarily have a postprandial effect but also show statistically significant reductions in fasting glucose levels.[6] FPG and PPG are the essential components of lowering glycosylated hemoglobin ($HbA_{1c}$), and PPG has a greater effect on lowering $HbA_{1c}$ at values <8.5%.[7]

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**[END SIDEBAR]**

## DPP-4 Inhibitors Offer Comprehensive Glycemic Management

Glycemic control efforts should be directed at the multiple pathophysiological defects of T2D and involve routine assessment of $HbA_{1c}$, monitoring of daily blood glucose values, and treatment with combination regimens that target glucose levels both before and after meals. As monotherapy, DPP-4 inhibitors demonstrate reductions of approximately 0.5% to 0.8% in $HbA_{1c}$, with concomitant reductions in PPG and FPG (eg, PPG reductions of –43 to –45 mg/dL at 120 minutes of an oral glucose tolerance test [OGTT] and FPG reductions of –9 to –15 mg/dL with saxagliptin monotherapy).[8,9] Durability of that effect has been demonstrated with up to 2 years of treatment.[10,11] DPP-4 inhibitors added to other OADs with complementary mechanisms of action have been proven to be particularly effective in lowering all 3 glycemic parameters in multiple studies (**Table 2**), regardless of age (<65 and ≥65 years), gender, race/ethnicity, or

body mass index.[12-18] DPP-4 inhibitors are also effective when used concurrently (initial combination) with MET in drug-naïve patients, lowering $HbA_{1c}$ by as much as 2.5% with concomitant decreases in FPG and PPG (**Figure 2**) as demonstrated during a 3-hour OGTT.[19]

TOLERABILITY

DPP-4 inhibitors offer strategic advantages with regard to tolerability, including few side effects or drug interactions with commonly used agents as well as simple oral dosing. These agents have demonstrated low risk for hypoglycemia and are weight neutral.[8,20,21] Tolerability profiles have been shown to be similar in patients aged <65 years and older patients (aged ≥65 years) with vildagliptin monotherapy.[22] The incidence of discontinuation due to clinical adverse reactions has been shown to be similar to placebo.[5] Sitagliptin requires a 2-step dose reduction; one for moderate renal impairment and a second for severe impairment and end-stage renal disease patients.[5] Saxagliptin requires only a 1-step dose reduction.[7] DPP-4 inhibitors in combination with MET, an SU, or a TZD demonstrated favorable tolerability with an overall adverse event profile similar to monotherapy with MET, an SU, or a TZD.[13,16-19,23-26] Modest increases in hypoglycemic events have been shown in studies with DPP-4 inhibitors in combination with an SU,[17,27] whereas others have shown no increase in hypoglycemic events.[14] When used in combination with MET, gastrointestinal side effects are not increased above those seen with MET alone.[13]

## Conclusion

DPP-4 inhibitors are a new class of agents that improve long-term, 24-hour control of $HbA_{1c}$, FPG (before meal) levels, and PPG (after meal) levels through decreased DPP-4–mediated degradation of incretin hormones. DPP-4 inhibitors provide a complementary mechanism of action to existing OADs and demonstrate significant efficacy when added to MET, an SU, or a TZD, with a well-tolerated profile, including a low risk for hypoglycemia and weight neutrality. DPP-4 inhibitors have been studied in a broad range of patients and have demonstrated similar efficacy, regardless of age, gender, or race/ethnicity. These agents offer an important addition to the treatment of patients with T2D by providing another mechanism to address the multiple pathophysiological defects present in this disease.

## Disclosure

Dr. Cobble has served on advisory boards for Abbott, AstraZeneca, Bristol-Myers Squibb, and Eli Lilly and Company; is the Chief Medical Officer for Atherotech Cardiodiagnostic Lipid Company; and has served as a lecturer for Pri-Med and the American Diabetes Association.

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**Table 1. DPP-4 Inhibitor Status and Availability**

| Drug | Status | Trade name | Pharmaceutical Company |
|---|---|---|---|
| Alogliptin | Failed to gain approval | Not officially disclosed | Takeda Pharmaceutical Company Limited |
| Dutogliptin | Phase 3 | Not officially disclosed | Phenomix/Forest Research Institute |
| Linagliptin | Phase 3 | Ondero® | Boehringer Ingelheim |
| Saxagliptin | Approved in the United States | Onglyza™ | Bristol-Myers Squibb/AstraZeneca) |
| Sitagliptin | Approved in the United States and Europe | Januvia®, Janumet™ | Merck & Co., Inc. |
| Vildagliptin | Approved in Europe | Galvus® | Novartis Pharmaceuticals Corporation |

DPP-4, dipeptidyl peptidase-4.

**Table 2. DPP-4 Inhibitors in Combination with Other Oral Antidiabetic Drugs***

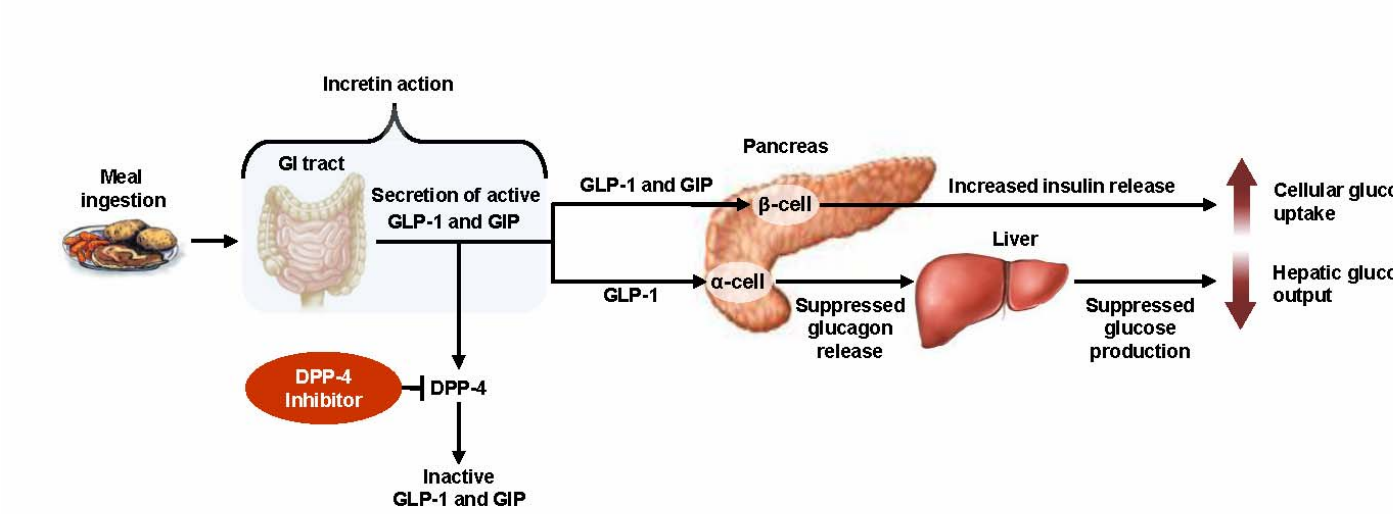
| Source | Therapy | Study Duration (wk) | No. of Patients† | Mean BL $HbA_{1c}$ % | Adjusted mean change from BL | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | $HbA_{1c}$ % | | FPG mg/dL | | 2-hr PPG mg/dL | |
| | | | | | Tx | PBO | Tx | PBO | Tx | PBO |
| **Alogliptin** Pratley et al, 2009[14] | Glyburide + alogliptin, 25 mg once daily | 26 | 500 | 8.1 | –0.53 | +0.01 | –8.4 | +2.2 | N/A | N/A |
| | Glyburide + alogliptin, 12.5 mg once daily | | | | –0.39 | | –4.7 | | N/A | |
| Nauck et al, 2009[13] | Metformin + alogliptin, 25 mg once daily | 26 | 527 | 7.9 | –0.6 | –0.1 | –17 | 0 | N/A | N/A |
| | Metformin + alogliptin, 12.5 mg once daily | | | | –0.6 | | –19 | | N/A | |
| Pratley et al, 2008[15] | Pioglitazone + alogliptin, 25 mg once daily | 26 | 493 | 8.0 | –0.80 | –0.19 | –19.9 | –5.7 | N/A | N/A |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Pioglitazone + alogliptin, 12.5 mg once daily | | | | –0.66 | | –19.7 | | N/A | |
| **Saxagliptin** DeFronzo et al, 2009[16] | Metformin + saxagliptin, 5 mg once daily | 24 | 370 | 8.0 | –0.69 | 0.13 | –22 | 1.2 | –58.2 | –18 |
| Hollander et al, in press[18] | Pioglitazone or rosiglitazone + saxagliptin, 5 mg once daily | 24 | 370 | 8.3 | –0.94 | –0.3 | –17.3 | –2.8 | –64.6 | –14.6 |
| Chacra et al, 2009[17] | Glyburide + saxagliptin, 5 mg once daily | 24 | 520 | 8.5 | –0.64 | 0.08 | –10 | 1.0 | –34 | 8.0 |
| **Sitagliptin** Charbonnel et al, 2006[23] | Metformin + sitagliptin, 100 mg once daily | 24 | 701 | 8.0 | –0.67 | –0.2 | –16.2 | 9.0 | N/A | N/A |
| Rosenstock et al, 2006[25] | Pioglitazone + sitagliptin, 100 mg once daily | 24 | 353 | 8.1 | –0.85 | –.15 | –16.7 | 1.0 | N/A | N/A |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Hermansen et al, 2007[27] | Glimepiride + sitagliptin, 100 mg once daily | 24 | 212 | 8.4 | –0.30 | 0.27 | –0.88 | 18.4 | –24.4 | 10.7 |
| **Vildagliptin** Garber et al, 2007[24] | Pioglitazone + vildagliptin, 50 mg twice daily | 24 | 463 | 8.7 | –1.0 | –0.3 | –19.8 | –9 | –46.8 | N/A |
| | Pioglitazone + vildagliptin, 50 mg once daily | | | | –0.8 | | –14.4 | | –34.2 | |
| Bosi et al, 2007[26‡] | Metformin + vildagliptin, 50 mg twice daily | 24 | 544 | 8.4 | –1.1 | | –31 | | –41 | |
| | Metformin + vildagliptin, 50 mg once daily | | | | –0.7 | | –14 | | –34 | |

BL, baseline; DPP-4, dipeptidyl peptidase-4; $HbA_{1c}$, glycosylated hemoglobin; FPG, fasting plasma glucose; PBO, placebo; PPG, postprandial glucose; Tx, treatment.
*To date, no head-to-head trials with DPP-4 inhibitors have been published.
†Includes placebo group.
‡Values represent placebo-adjusted mean change from baseline. Adjusted mean change from baseline values for vildagliptin treatment groups were not reported.

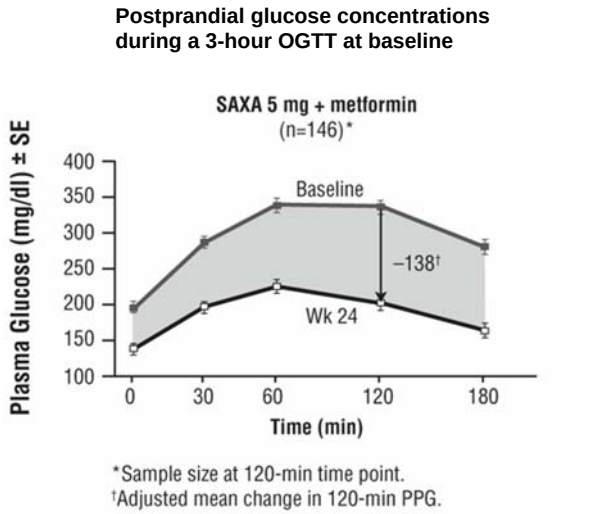
**Figure 1.** DPP-4 Inhibitors: Mechanism of Glucose Control[28]




DPP-4, dipeptidyl peptidase-4; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

Post–meal ingestion, GLP-1 and GIP are released from the small intestine and are rapidly degraded by the enzyme DPP-4. Inhibition of DPP-4 prevents the breakdown of GLP-1 and GIP and enhances glucose-stimulated insulin secretion (incretin action). GLP-1 and GIP act on the pancreatic β-cell to increase insulin release. GLP-1 also acts on the α-cell to suppress glucagon release and ultimately suppress hepatic glucose production. Together, the increased cellular glucose uptake and the decreased hepatic glucose output offer physiologic glucose control.

**Figure 2. Changes in Glucose After 24 Weeks of Saxagliptin and Metformin Initial Combination Therapy[19]**



FPG, fasting plasma glucose; MET, metformin; OGTT, oral glucose tolerance test; PPG, postprandial glucose; SAXA, saxagliptin.

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