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Sitagliptin

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Contents

Abstract

▲ Sitagliptin, an oral dipeptidyl peptidase-4 (DPP-4) inhibitor, improves glycaemic control by inhibiting DPP-4 inactivation of the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide. This increases active incretin and insulin levels, and decreases glucagon levels and post-glucose-load glucose excursion.

▲ In large, well designed phase III trials in patients with type 2 diabetes mellitus, sitagliptin 100 or 200mg once daily alone or in combination with other antihyperglycaemics was associated with significant improvements relative to placebo in overall glycaemic control and indices for insulin response and β-cell function.

▲ Improvements from baseline in mean glycosylated haemoglobin (HbA_{1c}) were significantly greater with sitagliptin monotherapy than with placebo in patients with type 2 diabetes.

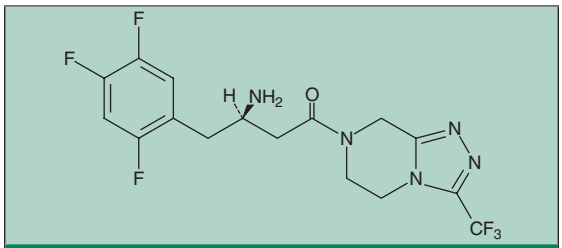
▲ As add-on therapy in patients with suboptimal glycaemic control despite oral antihyperglycaemic treatment, sitagliptin improved HbA_{1c} to a significantly greater extent than placebo when added to metformin or pioglitazone and was noninferior to glipizide when added to metformin.

▲ Sitagliptin was well tolerated when administered alone or in combination with other antihyperglycaemics, with an adverse event profile similar to that shown with placebo.

▲ The incidence of hypoglycaemia with sitagliptin was similar to that with placebo and, in combination with metformin, lower than that with glipizide.

▲ Sitagliptin had a generally neutral effect on bodyweight.

Features and properties of oral sitagliptin (Januvia™)	
Indication	
As an adjunct to diet and exercise to improve glycaemic control in adult patients with type 2 diabetes mellitus as monotherapy or combination therapy with metformin or a thiazolidinedione	
Mechanism of action	
Inhibits dipeptidyl peptidase-4, thereby slowing the inactivation of the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, which results in glucose-dependent increased insulin release and decreased glucagon levels	
Dosage and administration	
Usual dose	100mg
Frequency of administration	Once daily
Pharmacokinetic profile (single oral dose of 100mg in healthy volunteers)	
Mean peak plasma concentration (C_{max})	950 nmol/L
Mean area under the plasma concentration-time curve	8.52 μmol • h/L
Median time to C_{max}	1–4h
Mean apparent terminal half-life	12.4h
Most common adverse events in clinical trials	
Reported in ≥5% of patients and more commonly than with placebo	Upper respiratory tract infection, nasopharyngitis, headache



Sitagliptin

A fundamental component of the management of type 2 diabetes mellitus is improving glycaemic control, as this reduces the risk of microvascular and neuropathic complications of diabetes.[1,2] To achieve improved glycaemic control, management generally involves lifestyle modification (e.g. dietary change and exercise) and therapy with one or more oral antihyperglycaemic agents, with many patients eventually requiring insulin as the disease progresses.[1,3]

Several oral antihyperglycaemic agents (e.g. metformin, sulfonylureas, meglitinides, thiazolidinediones and α-glucosidase inhibitors) are currently available. However, there is a need for novel antihyperglycaemic agents with different mechanisms of action from existing oral antihyperglycaemics, as existing agents are often associated with an increased risk of adverse events (such as hypoglycaemia and bodyweight gain), typically become less effective over time as patients undergo the progressive β-cell failure characteristic of type 2 diabetes, and often fail to achieve glycaemic control in patients even when used as combination therapy.[2,4]

The gastrointestinal incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), have been the focus of recent diabetes research.[4-8] GLP-1 and GIP, which are released in response to the ingestion of food, enhance glucose-dependent insulin response and suppress glucagon response.[4-8] They also increase β-cell function and, in animals, β-cell mass. However, GLP-1 and GIP are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4).[4-8]

In patients with type 2 diabetes relative to individuals with normal glucose tolerance, postprandial levels of GLP-1 are reduced,[9] although the insulinotropic response to GLP-1 is maintained.[10] In contrast, GIP levels are maintained in patients with type 2 diabetes,[9] but its effect on insulin release response is impaired.[10] Although GLP-1 analogues (e.g. exenatide) also target incretin activity by increasing the metabolic stability of GLP-1, they require subcutaneous administration and cause gastrointestinal adverse effects.[8,11] DPP-4 inhibitors are a new class of antihyperglycaemics that slow the inactivation of GLP-1 and GIP, are unlikely to cause hypoglycaemia, may have beneficial effects on β-cell function and can be administered orally.[5,8]

Sitagliptin (Januvia™)[1] is the first DPP-4 inhibitor to be approved. This article examines the pharmacological properties of oral sitagliptin and its clinical use in patients with type 2 diabetes.

1. Pharmacodynamic Profile

An overview of the pharmacodynamic activity of sitagliptin, focusing on data in patients with type 2 diabetes where available, is provided in this section. Well designed pharmacodynamic studies (n = 32–70) were conducted in healthy[12,13] or middle-aged, obese, nondiabetic volunteers,[14] or patients with type 2 diabetes (glycosylated haemoglobin [HbA_{1c}] 6.5–11%) not receiving antihyperglycaemic agents.[15] The effects of sitagliptin on pharmacodynamic parameters in clinical phase III trials in patients with type 2 diabetes are presented in section 3.

- Sitagliptin inhibits DPP-4, thereby slowing the rapid inactivation of the endogenous incretin hormones GLP-1 and GIP. This inhibition increases and prolongs active incretin levels, resulting in glucose-dependent increases in insulin release and decreases in glucagon levels.[4,5]
- Sitagliptin is highly selective (>2600-fold) for DPP-4 over the structurally related enzymes DPP-8

1 The use of trade names is for product identification purposes only and does not imply endorsement.

or DPP-9 (50% inhibitory concentration 18 vs 48 000 and >100 000 nmol/L)[16] and has not been associated with toxicity related to DPP-8 or DPP-9 inhibition.[17] DPP-4 has enzymatic activity throughout the body, including playing a role in the immune system.[5] Although DPP-4 inhibition *in vivo* has not yet been associated with outcomes involving substrates of DPP-4 (e.g. effects involving stabilisation of growth hormone-releasing hormone, resulting in increases in insulin-like growth factor [IGF]-1 and IGF binding protein 3),[13,14] further study is required.

- Sitagliptin inhibits DPP-4 activity in a dose-dependent manner[12,13,15] and to a significantly greater extent than placebo.[12-15] In a single-dose crossover study in 58 patients with type 2 diabetes,[15] plasma DPP-4 activity was inhibited by 80% and 47% at 2 and 24 hours after sitagliptin 25mg administration, and by 96% and 80% at the corresponding time-points after sitagliptin 200mg administration. Over the 24-hour period, inhibition of DPP-4 activity was significantly greater with sitagliptin 25 or 200mg than with placebo (68.1% and 91.4% vs 2.1%; both $p < 0.001$).[15]

- Postprandial incretin levels are approximately doubled with sitagliptin ≥12.5mg.[12-15] Weighted average active GLP-1 and GIP levels increased ≈2-fold with sitagliptin 25 or 200mg relative to those with placebo during an oral glucose tolerance test (OGTT) 2 hours postdose in the crossover study.[15] For the 200mg dose, this doubling of active GLP-1 and GIP remained at 24 hours postdose during either an OGTT or meal tolerance test. The enhanced incretin levels result from inhibiting degradation of active GLP-1 and GIP and not by increasing secretion of the incretins, as evidenced by increases in the active **:** total GLP-1 or GIP ratios and reductions in total GLP-1 or GIP levels.

- Post-OGTT glucose excursion is reduced with sitagliptin in patients with type 2 diabetes[15] and in obese nondiabetic patients.[14] In the crossover study,[15] sitagliptin 200mg reduced glucose excursion following an OGTT by 26% at 2 hours postdose and by 18% at 24 hours postdose relative to placebo (both $p \leq 0.001$). Glucose excursion was reduced to a significantly greater extent with sitagliptin 25mg than placebo following an OGTT at 2 hours postdose (22% reduction; $p \leq 0.001$), but not at 24 hours (9% reduction).[15]

- Sitagliptin is associated with postprandial changes in glucoregulatory hormones in patients with type 2 diabetes.[15] After a 2-hour postdose OGTT, significant ($p < 0.05$) increases in insulin (21% and 22%) and C-peptide levels (13% and 21%), and significant decreases in glucagon levels (7% and 14%) were shown with sitagliptin 25 or 100mg relative to placebo in type 2 diabetic patients in the crossover study.[15] As expected, changes in glucose, insulin, glucagon or C-peptide levels with sitagliptin were not significant in studies in healthy volunteers.[12,13,15]

2. Pharmacokinetic Profile

This section briefly summarises the pharmacokinetic properties of oral sitagliptin, focusing on the approved adult dose (100mg) where possible. Pharmacokinetic studies were conducted in healthy[12,13,18-23] and/or obese[14,23] volunteers (n = 8–70), or patients with type 2 diabetes (n = 58[15] or 13[24]), renal dysfunction (n = 24)[25] or moderate hepatic insufficiency (n = 20).[26] Some studies are available only as abstracts.[18-20,22,23,25-27] Additional data were obtained from the manufacturer's prescribing information.[28]

- Sitagliptin is rapidly absorbed after oral administration, with an absolute bioavailability of ≈87%.[28] Coadministration of a high-fat meal does not affect the pharmacokinetics of sitagliptin.[12]

- After administration of single-dose sitagliptin 100mg in healthy volunteers, mean maximum plasma concentrations (C_{max}) of 950 nmol/L were achieved in a median time (t_{max}) of 1–4 hours and the mean area under the plasma concentration-time curve (AUC) was 8.52 μmol • h/L.[28] The AUC for sitagliptin increased in an approximately dose-proportional manner with increasing single doses of 1.5–800mg[12,13] or multiple doses of 25–600 mg/day.[13]

- In healthy volunteers, the mean volume of distribution at steady state is ≈198L after a single intrave-

nous dose of sitagliptin 100mg.[28] Thirty-eight percent of sitagliptin is reversibly bound to plasma proteins.[28]

- Sitagliptin undergoes primarily renal elimination (≈79% is excreted unchanged in the urine), involving active tubular secretion and possibly human organic anion transporter-3 and/or p-glycoprotein transport.[28]
- The apparent terminal half-life ($t_{1/2}$) of single-dose sitagliptin 100mg in healthy volunteers was 12.4 hours, with renal clearance of ≈350 mL/min. Within 1 week after administration of a single radiolabelled dose in healthy volunteers, 87% of the administered radioactivity was eliminated in the urine and 13% in the faeces.
- Sitagliptin undergoes limited metabolism primarily by cytochrome P450 (CYP) 3A4, with contribution from CYP2C8.[28,29] Metabolites, which accounted for ≈16% of the radioactivity after administration of a radiolabelled dose in healthy volunteers, are not expected to have DPP-4 inhibitory activity.[28]
- The pharmacokinetic and pharmacodynamic profile of sitagliptin is consistent with once-daily administration.[12,13] At steady-state (sitagliptin 100mg once daily for 10 days), the values for the primary pharmacokinetic parameters (AUC, C_{max}, t_{max} and $t_{1/2}$) were statistically similar to those at day 1 (single 100mg dose), with day 10 : day 1 AUC accumulation ratios of 1.05–1.29.[13]
- In patients with type 2 diabetes, the pharmacokinetic profile of sitagliptin is generally similar to that in healthy volunteers.[12,15,28] After a single 200mg dose, mean AUC from time zero to 24 hours was 14.10 μmol • h/L, mean C_{max} was 1923 nmol/L, median t_{max} was 2 hours and mean $t_{1/2}$ was 11.0 hours.[15]
- Age,[23] gender,[23] body mass index (BMI)[14,23] and/or race[28] do not appear to significantly alter the pharmacokinetics of single-[23] or multiple-dose[14] sitagliptin.
- In patients with renal impairment receiving single-dose sitagliptin 50mg, creatinine clearance (CL_{CR}) was inversely related to the AUC from time zero to infinity (AUC_∞) of sitagliptin and approximately proportional to its renal clearance.[25] Relative to healthy controls, sitagliptin AUC_∞ values were 1.6-, 2.3-, 3.8- and 4.5-fold higher in patients with mild (CL_{CR} 1.8 to <4.8 L/h [50 to <80 mL/min]), moderate (CL_{CR} 1.8 to <3.0 L/h [30 to <50 mL/min]), severe (CL_{CR} <1.8 L/h [<30 mL/min]) or end-stage renal disease (ESRD) requiring haemodialysis, respectively.
- Moderate hepatic impairment (Child-Pugh score 7–9) does not appear to significantly alter the pharmacokinetics of sitagliptin.[26]
- Sitagliptin is considered unlikely to interact with drugs utilizing CYP3A4, CYP2C8, CYP2C9, CYP2D6, CYP1A2, CYP2C19 or CYP2B6 metabolism, or organic cationic or p-glycoprotein transport, or to have interactions mediated by plasma protein binding displacement.[28]
- *In vivo,* no clinically relevant pharmacokinetic interactions requiring dose adjustment were observed during coadministration of sitagliptin and simvastatin,[18] rosiglitazone,[21] warfarin,[19] glibenclamide (glyburide),[22] metformin[24] digoxin,[20] ciclosporin[27] or oral contraceptives (norethisterone [norethindrone] or ethinylestradiol).[28]

3. Therapeutic Efficacy

The efficacy of oral sitagliptin as monotherapy[30-35] or in combination with pioglitazone[36] or metformin[37-39] in the treatment of patients with type 2 diabetes has been investigated in randomised, double-blind, controlled, multicentre trials. Most studies have been fully published;[31,33,34,36-39] data from other studies are available as abstracts,[30,35] or an abstract plus oral presentation.[32] Additional data were obtained from the manufacturer's prescribing information.[28]

Patients were randomised to monotherapy with sitagliptin or placebo in two phase II dose-ranging studies of sitagliptin 10–100 mg/day for 12 weeks (n = 552[30] and 743[31]), a phase II trial of sitagliptin 100mg once daily for 12 weeks in Japanese patients (n = 151),[32] two large phase III trials of sitagliptin 100 or 200mg once daily for 18 weeks (n = 521)[33] or 24 weeks (n = 741),[34] and a 12-week phase III trial of dosage-adjusted sitagliptin in patients with

renal impairment (n = 91).[35] Although not designed as a noninferiority trial, patients received glipizide as a benchmark therapy in one dose-ranging trial.[31]

An 8-week crossover trial[37] and two 24-week phase III trials evaluated the efficacy of adding randomised treatment with sitagliptin (50 mg twice daily[37] or 100mg once daily[36,38]) or placebo to the treatment of patients with inadequate glycaemic control with pioglitazone (35–40 mg/day) [n = 353][36] or metformin (≥1500 mg/day) [n = 28[37] and 701[38]]. The comparative efficacy of adding sitagliptin 100mg once daily or glipizide (up to 20 mg/day) to metformin in patients with inadequate glycaemic control was investigated in a 52-week phase III trial (per-protocol n = 793).[39]

Where stated, trials had a diet/exercise run-in period with drug washout (for patients who were receiving oral antihyperglycaemic therapy when they entered the study)[30-38] and/or metformin or pioglitazone monotherapy titration/stabilisation[36,38,39] followed by a 2-week, single-blind placebo lead-in period.[31-34,36,38,39] Patients who met the HbA_{1c} entry criteria (6.5–10%[30-32,35,37,39] or 7–10%[33,34,36,38]) were randomised to one of the treatment arms. Patients were allowed rescue treatment with metformin[33,34,36] or pioglitazone[38] depending on prespecified glycaemic criteria in most phase III trials.

Mean baseline values, where reported, were patient age 54–57[31-34,36-39] or 68[35] years; duration of diabetes 4.0–6.8 years;[31-34,36-39] baseline HbA_{1c} 6.5–9.6%;[30-39] and fasting plasma glucose (FPG) 8.4–10.1 mmol/L.[31-34,36-39]

The most commonly stated primary efficacy endpoint was the change from baseline in HbA_{1c}.[30-34,36,38,39] Other efficacy endpoints included the proportion of patients achieving HbA_{1c} goals, and changes from baseline in other measures of glycaemic control or pharmacodynamic parameters.

Where stated, analyses were based on the all-patients-treated (excluding data obtained after glycaemic rescue where applicable),[31,33,34,36,38] modified intention-to-treat with last observation carried forward[30,32] or per-protocol[39] populations. This section focuses primarily on results from fully published phase III trials.[33,34,36,38,39]

Effects on Glycaemic Control

Monotherapy

- Sitagliptin monotherapy is effective in patients with type 2 diabetes, producing significant improvements relative to placebo in HbA_{1c} and other markers of glycaemic control.[30-34] Sitagliptin 200mg once daily did not offer any efficacy advantages over sitagliptin 100mg once daily.[33,34] The differences between the sitagliptin 100 and 200mg treatment groups were small across all efficacy endpoints and did not show a consistent benefit for the higher over the lower dosage.[33,34]
- In the two dose-ranging studies in patients with type 2 diabetes,[30,31] sitagliptin 10–100 mg/day improved glycaemic control in a dose-dependent manner. After 12 weeks, placebo-subtracted changes from baseline in mean HbA_{1c} ranged from −0.4%[30,31] with sitagliptin 25mg once daily to −0.6%[30] or −0.8%[31] with sitagliptin 100 mg/day and, in the trial with the glipizide arm,[31] −1.0% with glipizide (5mg titrated to 10, 15 or 20 mg/day). Dose-dependent reductions with sitagliptin were also shown for other glycaemic endpoints, including FPG, fructosamine and mean daily glucose levels.[30,31]
- In the 12-week, phase II trial in Japanese patients,[32] improvements from baseline in HbA_{1c} and 2-hour postprandial plasma glucose (PPG) were significantly ($p < 0.001$) greater with sitagliptin 100mg once daily than with placebo (−0.65% vs +0.41% and −3.8 vs +0.7 mmol/L). A significantly greater proportion of sitagliptin than placebo recipients achieved the goal of HbA_{1c} <7% (58.1% vs 14.5%; $p < 0.001$).[32]
- At the end of the phase III trials, HbA_{1c} was significantly ($p < 0.001$) lower with sitagliptin than with placebo (figure 1a).[33,34] Placebo-corrected mean HbA_{1c} changes from baseline with sitagliptin 100mg once daily were −0.60% (95% CI −0.82, −0.39) in the 18-week trial[33] and −0.79% (95% CI −0.96, −0.62) in the 24-week trial.[34] The corre-

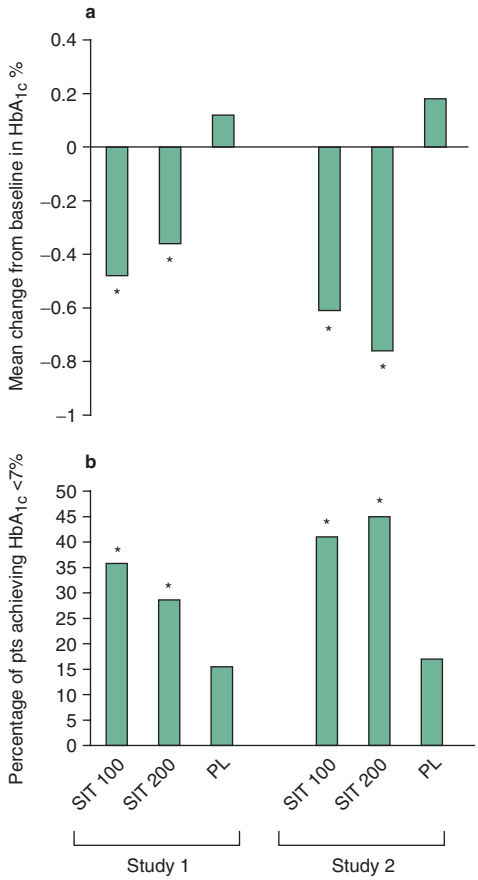


Fig. 1. Efficacy of oral once-daily sitagliptin (SIT) monotherapy in patients (pts) with type 2 diabetes mellitus. (**a**) Mean change from baseline in glycosylated haemoglobin (HbA_{1c}) and (**b**) percentage of pts achieving HbA_{1c} <7% with SIT versus placebo (PL) in the all-patients-treated populations of two randomised, double-blind, multicentre trials.[33,34] Pts received: SIT 100mg (n = 193), SIT 200mg (n = 199) or PL (n = 103) for 18wk in study 1;[33] and SIT 100mg (n = 229), SIT 200mg (n = 238) or PL (n = 244) for 24wk in study 2.[34] * p < 0.001 vs PL.

sponding values for sitagliptin 200mg once daily in the 18- and 24-week trials were −0.48% (95% CI −0.70, −0.26)[33] and −0.94% (95% CI −1.11, −0.77).[34]

- Sitagliptin was associated with better achievement of glycaemic control goals.[33,34] Significantly (p < 0.001) greater proportions of patients achieved the goal of HbA_{1c} <7% with sitagliptin than with placebo (figure 1b).[33,34]

- In subgroup analyses, patients with higher baseline HbA_{1c} (i.e. ≥9%) experienced statistically significantly greater reductions in HbA_{1c} than those with lower baseline HbA_{1c} in one trial,[34] but not in the other.[33] In patients with baseline HbA_{1c} values of ≥9%, 8% to <9% and <8%, placebo-subtracted HbA_{1c} reductions for sitagliptin 100mg once daily were −1.20%, −0.61% and −0.44% (no significant difference) in the 18-week trial[33] and −1.52%, −0.80% and −0.57% (p < 0.001) in the 24-week trial.[33]

- The efficacy of sitagliptin on lowering HbA_{1c} was consistent across subgroups (e.g. not affected by gender, age, race, prior use of oral antihyperglycaemic agents, or baseline BMI, insulin resistance, β-cell function or metabolic syndrome status).[33,34]

- Significant (p ≤ 0.01) improvements in FPG were also shown with sitagliptin.[33,34] Sitagliptin 100 or 200mg once daily was associated with placebo-subtracted mean changes from baseline in FPG of −1.1 (95% CI −1.7, −0.5) and −0.9 (95% CI −1.5, −0.3) mmol/L in the 18-week trial[33] and −1.0 mmol/L (95% CI −1.0, −0.4) and −1.2 mmol/L (95% CI −1.2, −0.7) in the 24-week trial.[34]

- Sitagliptin significantly (p ≤ 0.01) improved 2-hour PPG values.[33,34] Placebo-subtracted mean changes from baseline in 2-hour PPG with sitagliptin 100 or 200mg once daily were −2.6 (95% CI −4.2, −1.0) and −2.9 (95% CI −4.6, −1.3) mmol/L in the 18-week trial,[33] and −2.7 (95% CI −3.2, −2.2) and −3.1 (95% CI −3.6, −2.6) mmol/L in the 24-week trial.[32,34]

- In the phase III trials,[33,34] sitagliptin 100 or 200 mg/day generally improved postprandial AUCs for glucose, insulin and C-peptide, and insulin AUC : glucose AUC ratios to a significantly (p < 0.05) greater extent than placebo. Mean increases from baseline in levels of postprandial C-peptide were also significantly greater (p < 0.05) with sitagliptin than with placebo.[33]

- Fewer patients receiving sitagliptin than placebo required rescue therapy with metformin at pre-specified glycaemic thresholds.[33,34] The proportions of patients in the sitagliptin 100 or 200mg once daily or placebo groups that required metformin rescue ther-

apy were 8.8%, 11.7% and 17.3% (statistical significance not reported) in the 18-week trial,[33] and 8.8% and 4.8% versus 20.6% (both $p < 0.001$) in the 24-week trial.[34]

- In the trial in type 2 diabetic patients with chronic renal impairment, improvements in glycaemic control with dose-adjusted sitagliptin (50mg once daily in patients with moderate renal impairment and 25mg once daily in those with severe renal impairment or ESRD requiring haemodialysis; see section 5) were similar to those in patients without renal impairment in the pivotal trials.[35] Mean changes from baseline with sitagliptin and placebo were −0.59% versus −0.18% for HbA_{1c}, and −1.4 versus −0.2 mmol/L for FPG (pooled results for both dosages; statistical significance not reported).

Combination Therapy

- The addition of sitagliptin 100 mg/day to pioglitazone[36] or metformin[37-39] provides more effective glycaemic control than either drug alone[36-38] and similar efficacy to the addition of glipizide[39] in patients with inadequately controlled type 2 diabetes.
- At the end of the 24-week trials, HbA_{1c} was significantly ($p < 0.001$) lower with the addition of sitagliptin 100mg once daily to pioglitazone or metformin than with the addition of placebo (figure 2a). The placebo-corrected changes in mean HbA_{1c} were −0.70% (95% CI −0.85, −0.54) with sitagliptin plus pioglitazone,[36] and −0.65% (95% CI −0.77, −0.53) with sitagliptin plus metformin.[38]
- Sitagliptin 100 mg once daily was as effective as glipizide (mean dosage 10.3 mg/day) when added to metformin treatment.[39] Sitagliptin met pre-specified limits for non-inferiority with regard to changes from baseline in HbA_{1c} relative to glipizide at 52 weeks; the upper limit of the 95% confidence interval for the between-group difference was 0.08, which was less than the prespecified limit of 0.3. The mean change from baseline in HbA_{1c} was −0.67% for both groups (figure 2a; $p < 0.001$ vs baseline for both).[39]
- The addition of sitagliptin 100mg once daily to pioglitazone[36] or metformin[38] approximately doubled the number of patients achieving the glycaemic control goal of HbA_{1c} <7% relative to the addition of placebo ($p < 0.001$; figure 2b) in the 24-week trials.[36,38] The proportion of patients achieving HbA_{1c} <7% with the addition of sitagliptin to metformin was similar to that with the addition of glipizide in the 52-week trial (figure 2b).[39]
- FPG levels improved to a significantly ($p \leq 0.001$) greater extent with the addition of sitagliptin 100mg once daily to pioglitazone[36] or metformin[38] than with the addition of placebo, and to a similar extent with sitagliptin and glipizide when added to metformin.[39] Placebo-subtracted

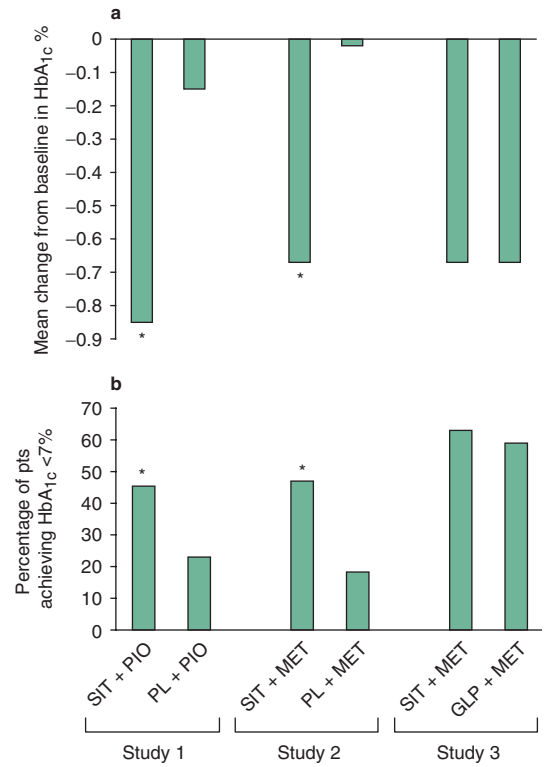


Fig. 2. Efficacy of oral once-daily sitagliptin 100mg (SIT) in combination with pioglitazone (PIO) or metformin (MET) in patients (pts) with type 2 diabetes mellitus. (**a**) Mean change from baseline in glycosylated haemoglobin (HbA_{1c}) and (**b**) percentage of pts achieving HbA_{1c} <7% with SIT versus placebo (PL)[36,38] or glipizide (GLP)[39] in the all-patients-treated[36,38] or per-protocol[39] populations of three randomised, double-blind, multicentre trials. Pts received: SIT plus PIO (n = 175), PL plus PIO (n = 178) for 24wk in study 1;[36] SIT plus MET (n = 229) or PL plus MET (n = 244) for 24wk in study 2;[38] and SIT plus MET (n = 382) or GLP plus MET (n = 411) for 52wk in study 3.[39] * p 0.001 vs comparator.

mean changes from baseline in FPG were −1.0 mmol/L (95% CI −1.3, −0.6) with sitagliptin plus pioglitazone,[36] and −1.4 mmol/L (95% CI −1.7, −1.1) with sitagliptin plus metformin.[38] In the 52-week trial, changes from baseline in FPG with the addition of sitagliptin to metformin therapy were similar to those with the addition of glipizide (−0.6 vs −0.4 mmol/L).[39]

- In the 24-week trial, when added to metformin, sitagliptin 100mg once daily was also associated with significant ($p < 0.05$) mean changes from baseline relative to placebo in levels of fasting insulin and C-peptide; 2-hour PPG, insulin and C-peptide; 2-hour postprandial total AUCs for glucose, insulin and C-peptide; and 2-hour post-prandial insulin AUC : glucose AUC ratios.[38]
- Glycaemic rescue therapy was required by fewer patients receiving sitagliptin than those receiving placebo in addition to pioglitazone (7% vs 14%; statistical significance not reported)[28] or metformin (4.5% vs 13.5%; $p < 0.001$).[38]

Effects on β-Cells and Insulin Sensitivity

- Sitagliptin appears to improve β-cell function. In a C-peptide minimal model using meal-tolerance test data from three phase III trials,[33,34,38] relative to placebo, sitagliptin alone or as add-on therapy to metformin significantly improved β-cell responsiveness to basal glucose concentrations and above-basal glucose concentrations following a meal, as well as the overall responsiveness of the β-cell to glucose (p-values not reported; available as an abstract).[40]
- In phase III trials, improvements in β-cell function with sitagliptin as monotherapy[33,34] or as add-on therapy to metformin[38] or pioglitazone,[36] were also indicated by significant ($p < 0.05$) reductions with sitagliptin relative to placebo in fasting proinsulin : insulin ratios[33,34,36,38] and/or fasting serum proinsulin levels.[36] With the exception of one trial,[36] improvements in homeostasis model assessment β-cell function (HOMA-β) were significantly greater with sitagliptin than with placebo.[33,34,38]
- The effect of sitagliptin on insulin sensitivity requires further study, as responses have been mixed in phase III trials. Relative to placebo, sitagliptin as monotherapy[33,34] or as add-on therapy to pioglitazone[36] did not significantly improve insulin sensitivity (assessed by the homeostasis model assessment of insulin resistance [HOMA-IR] and/or quantitative insulin sensitivity check index [QUICKI]);[33,34,36] the addition of sitagliptin to metformin significantly ($p < 0.05$) improved QUICKI, but not HOMA-IR.[38]
- In the 52-week comparative trial, when added to metformin, there were no significant differences between sitagliptin and glipizide in parameters measuring β-cell function or insulin sensitivity (i.e. fasting serum proinsulin levels, fasting proinsulin : insulin ratio, HOMA-β, HOMA-IR and QUICKI).[39]

4. Tolerability

This section focuses on the tolerability of the approved dosage of oral sitagliptin 100mg once daily. Data are available from the phase III trials (section 3)[33,34,36,38,39] and the manufacturer's prescribing information,[28] which presents pooled results from the pivotal trials.[33,34,36,38] Only descriptive analyses were generally reported.

- Sitagliptin is well tolerated in patients with type 2 diabetes,[33,34,36,38,39] including those with renal impairment.[35] Sitagliptin 100 or 200mg once daily administered alone[32-34] or in combination with metformin[38,39] or pioglitazone[36] had an adverse event profile similar to that of placebo.
- In pivotal phase III trials, the only adverse events reported in ≥5% of recipients of sitagliptin 100mg once daily and more commonly with sitagliptin than with placebo were nasopharyngitis (5.2% vs 3.3%) with monotherapy, and upper respiratory tract infection (6.3% vs 3.4%) and headache (5.1% vs 3.9%) with pioglitazone combination therapy.[28]
- Sitagliptin mono- or combination therapy does not increase the risk of hypoglycaemia.[28,32-34,36,38] The proportion of patients experiencing at least one hypoglycaemic event regardless of severity with sitagliptin 100mg once daily was numerically similar to that with placebo (overall incidence in pooled data 1.2% vs 0.9%)[28] and, in combination with

metformin, significantly lower than that with glipizide (4.9% vs 32.0%; $p < 0.001$).[39]

- The incidence of gastrointestinal events was not increased with sitagliptin relative to placebo[28,32-34,36,38] or glipizide.[39] In pooled data, the incidences of selected gastrointestinal adverse events with sitagliptin 100mg once daily and placebo were 2.3% and 2.1% for abdominal pain, 1.4% and 0.6% for nausea and 3.0% and 2.3% for diarrhoea.[28]
- Mean changes in bodyweight are generally minimal with sitagliptin 100mg once daily.[32-34,36,38,39] Reductions from baseline in bodyweight with sitagliptin monotherapy were similar to (−0.7 vs −0.6kg[33]) or significantly less (−0.1 vs −1.1kg[34] and −0.2 vs −1.1kg;[32] both $p < 0.01$) than those with placebo. Sitagliptin was associated with similar changes from baseline in bodyweight as placebo when added to pioglitazone (1.8 vs 1.5kg)[36] or metformin (−0.6 to −0.7kg for both groups).[38] Moreover, the addition of sitagliptin to metformin was associated with weight loss (−1.5kg), whereas the addition of glipizide to metformin was associated with weight gain (+1.1kg) at 52 weeks in the comparative trial ($p < 0.001$).[39]
- Withdrawal rates due to drug-related adverse events were similar in patients treated with sitagliptin or placebo.[28] Where reported, the proportions of patients discontinuing sitagliptin 100mg once daily or placebo due to drug-related adverse events were 0.5% vs 2.7%,[33] 0.4% vs 0.8%,[34] 0.9% vs 0%[38] and 0.6% vs 0.6%.[36] In the all-patients-treated population of the 52-week comparative trial, 1.4% of patients in both the add-on sitagliptin and add-on glipizide groups discontinued treatment because of drug-related adverse events.[39]
- No clinically meaningful changes in vital signs, ECG and/or laboratory parameters were associated with sitagliptin 100mg once daily in clinical trials.[28,33,34,36,38,39]

5. Dosage and Administration

In adult patients with type 2 diabetes, the recommended dosage of sitagliptin is 100mg orally once daily, either as monotherapy or as combination therapy with metformin or a thiazolidinedione.[28] It may be taken with or without food.

Sitagliptin should not be used in the treatment of patients with type 1 diabetes or diabetic ketoacidosis. To obtain plasma concentrations similar to those in patients without renal impairment, the dosage of sitagliptin should be adjusted to 50mg once daily in patients with moderate renal impairment (CL_{CR} 1.8 to <3.0 L/h [30 to <50 mL/min]) and to 25mg once daily in those with severe renal impairment (CL_{CR} <1.8 L/h [<30 mL/min]) or ESRD requiring haemodialysis or peritoneal dialysis (section 2).[28] Local prescribing information should be consulted for further information regarding contraindications, precautions and drug interactions.

6. Sitagliptin: Current Status

In the US, oral sitagliptin is approved as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes. It is indicated for use as monotherapy or as combination therapy with metformin or a thiazolidinedione when monotherapy with these agents does not provide adequate glycaemic control. Sitagliptin is the first DPP-4 inhibitor to reach the market and, in well designed clinical trials, improved glycaemic control in patients with type 2 diabetes, both as monotherapy and in combination with metformin or pioglitazone. Its tolerability profile is generally similar to that of placebo. Clinical trials are ongoing to further characterise the efficacy and safety of sitagliptin in patients with type 2 diabetes.[41]

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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