Continuous glucose profiles with vildagliptin versus sitagliptin in add-on to metformin: Results from the randomized Optima study

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Abstract

Aim. – To compare continuous glucose monitoring (CGM) profiles on vildagliptin versus sitagliptin in addition to metformin, in patients with inadequately controlled type 2 diabetes mellitus (HbA1c, 6.5–8.0%).

Methods. – A multicenter, prospective, randomised, open-label study with blinded endpoint analysis. CGM data acquired over three days – firstly on metformin alone and then 8 weeks after the addition of either vildagliptin (n = 14) or sitagliptin (n = 16) –were blinded and analyzed centrally.

Results. – In comparable populations with a mean baseline HbA1c of 7.1%, 24-hour glucose variability – measured by mean amplitude of glucose excursions and standard deviation of mean glucose concentration – showed similar improvement on both drugs versus metformin alone. In contrast, a series of predefined parameters reflecting daily glycaemic control – mean 24-hour blood glucose concentration, and the times spent in the optimal glycaemic range (70–140 mg/dL) and above the hyperglycaemic thresholds of 140 and 180 mg/dL together with the corresponding AUC values – were significantly improved from baseline only in the vildagliptin arm. In addition, overall hyperglycaemia (AUC[24 h] >100 mg/dL) significantly dropped from baseline on vildagliptin [−37%] but not on sitagliptin [−9%], while postprandial hyperglycaemia (AUC[0–4 h] × 3) was significantly reduced on both, and basal hyperglycaemia (overall – postprandial hyperglycaemia was reduced only on vildagliptin [−41%; P = 0.04]).

Conclusions. – The addition of a DPP-4 inhibitor significantly reduced glycaemic variability with no difference between the two drugs. However, vildagliptin induced better circadian glycaemic control than sitagliptin with a significant decrease on overall hyperglycaemia, mainly driven by reduction on basal hyperglycaemia.

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Keywords: Type 2 diabetes mellitus; Vildagliptin; Sitagliptin; Continuous glucose monitoring; Circadian glycaemic profiles

Résumé

Étude randomisée Optima : comparaison par mesure continue du glucose de l’effet sur le profil glycéémique de la vildagliptine versus la sitagliptine en addition à la metformine.

Objectifs. – Comparer les profils glycéémiques nycthéméraux obtenus par enregistrement continu (CGM) avec vildagliptine versus sitagliptine, ajoutées à la metformine chez des patients diabétiques de type 2 insuffisamment contrôlés (HbA1c, 6.5–8.0%).

Méthodes. – Étude multicentrique, prospective, randomisée, en ouvert, avec analyse en insu du critère primaire (données CGM). Les profils glycéémiques ont été enregistrés sur trois jours, initialement sous metformine seule puis huit semaines après l’ajout de vildagliptine (n = 14) ou sitagliptine (n = 16) et analysés de façon centralisée.

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1. Introduction

Drugs targeting a variety of systems are used to manage type 2 diabetes mellitus (T2DM) [1]. The gliptins, a relatively new class of oral antidiabetic, act by inhibiting dipeptidyl peptidase-4 (DPP-4) which inactivates the incretins, namely gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) [2]. The net result of prolonged incretin action is improved glucose control [3] associated with increased α and β-cell sensitivity to glucose [4]. This makes this novel class a good candidate for adjunctive treatment to metformin to enhance glycaemic control without inducing weight gain or causing episodes of hypoglycaemia [5]. The results of two recent pilot studies [6,7] suggested that therapeutic agents that act on the incretin system modulate not only chronic hyperglycaemia but also daily glucose profiles and variability. It has been suggested that acute temporal fluctuations in blood glucose concentration may trigger oxidative stress [8] and thus be a pathogenic determinant in diabetes [9–11].

The two most widely used gliptins, sitagliptin and vildagliptin, are chemically distinct species with different characteristics of binding to DPP-4: whereas the former is a competitive inhibitor, the latter acts as a substrate for the enzyme forming a reversible covalent complex with the catalytic site of DPP-4 that dissociates slowly, eliciting prolonged DPP-4 inhibition despite a rather short half-life of about 2 to 3 hours [12]. This raises intact GLP-1 levels, not only after meal ingestion but also in the fasting state [13–16] and maintains suppressed glucagon levels and decreased hepatic glucose production overnight [16]. However, the implications of such pharmacodynamic differences have largely remained unexplored. The clinical efficacy of the various DPP-4 inhibitors generally appears to be similar [17] but vildagliptin and sitagliptin have never been compared in a head-to-head randomised clinical trial in patients with T2DM.

Classically, glucose control in diabetes is assessed by measuring HbA1c three or four times a year, possibly complemented with the occasional SMBG monitoring of fasting blood glucose levels and postprandial excursions. Much of our understanding of the pathogenesis of diabetes comes from such low-resolution information which ignores factors that are more difficult to monitor even though they may be important [18,19]. The effects of daily fluctuations in blood glucose concentration are not necessarily reflected in HbA1c levels although they may be related to impaired β cell function [20], changes in postprandial insulin and glucagon secretion, and oxidative stress [21,22]. How this correlates with glucose control as traditionally evaluated by HbA1c level [23] can now be investigated using continuous glucose monitoring (CGM) which yields high-resolution data on how blood glucose concentration reacts to exercise, food, medications and other factors [24]. Thus, this new tool sheds light on changes that are subtler and shorter-term than can be evaluated using the traditional surveillance modalities, in particular data on circadian glycaemic profiles and 24-hour glycaemic control. Since the first CGM system was licensed in 1999, numerous studies have been conducted to monitor glucose profiles in type 1 diabetics, especially children, type 2 treated with insulin and pregnant women but relatively few studies have focused on type 2 diabetic patients on oral antidiabetic treatment [25,26]. The studies that have been carried have shown how 24-hour glycaemic profiles can be used to stage diabetes [27] provide teaching opportunities [28] and inform the therapeutic decision-making process [10,25,27].

In this randomised study, we set out to directly compare CGM profiles on two gliptins, vildagliptin and sitagliptin, in patients with T2DM which was not optimally controlled on metformin alone.

2. Methods

2.1. Study design and procedures

This pilot, multicenter, prospective, randomized, active-controlled study was conducted using Prospective Randomized Open Label with Blinded Endpoint (PROBE) methodology for the main efficacy end points (all CGM data). Patients were recruited at seven centres by diabetes specialists (five university hospitals and two private practices). Patients attended one Selection Visit (Week 2) where inclusion and exclusion criteria were assessed. They were provided with a glucose meter (Contour® Link Bayer/Medtronic) and shown how to use it for self-monitoring of blood glucose (SMBG). Eligible patients
were included after a 2-week-educational run-in period with laboratory testing. A first 72-hour CGM recording was performed while on metformin alone. Patients with a successful recording were then centrally randomized on a one-to-one basis to receive either vildagliptin (50 mg twice daily) or sitagliptin (100 mg once daily) for the next eight weeks, in addition to ongoing metformin (the dose of which remained unchanged). A second 72-hour CGM profile was then recorded after 8 weeks of add-on therapy.

2.2. Inclusion and exclusion criteria

Men and women (infertile or using a medically approved birth control method) of 18 to 80 years with a body mass index (BMI) of 22 to 45 kg/m², with T2DM (HbA1c 6.5–8.0%) on metformin for at least 3 months (a stable, maximum tolerated daily dose of at least 1500 mg), who were willing to perform SMBG at least 6 times daily and use the CGMS® (iPro™, Medtronic/MiniMed, Northridge, CA) for 3 consecutive days on two different occasions, were eligible to participate.

Patients with a history of type 1 diabetes or any secondary form of diabetes were excluded, as were those with acute metabolic diabetic complications within the past 6 months, an acute infection that might affect glucose control in the 4 weeks prior to visit 1, serious cardiac conditions, clinically significant liver or kidney disease, or ASAT/ALAT > 3 times the upper threshold (140 and 180 mg/dL) together with the corresponding area under the curve (AUC) values. Hypoglycaemia was defined as at least two consecutive CGM readings of < 70 mg/dL. In addition, areas under 24-hour glycaemic traces (AUCs) were analyzed to estimate: overall hyperglycaemia (defined as AUC ≥ 100 mg/dL over the full 24-hour period = AUCtotal); postprandial hyperglycaemia (AUC[0–4 h], i.e. for four-hour periods after each of the main meals and, if considered relevant by the core laboratory, after additional snacks = AUCpp); and basal hyperglycaemia, i.e. overall hyperglycaemia – postprandial hyperglycaemia (AUCb) as previously described in [30].

Secondary assessments addressed changes from baseline in HbA1c (with both measurements performed at the same local laboratory using a Diabetes Control and Complications Trial reference method), fasting plasma glucose (FPG) results and SMBG readings. All adverse events (AEs) and serious AEs (SAEs) together with their severity and relationship to the study treatment, were analyzed as well as episodes of symptomatic hypoglycaemia and changes in body weight.

2.3. Continuous glucose monitoring (CGM)

CGMS® (iPro™, Medtronic/MiniMed, Northridge, CA) measures the interstitial glucose concentration using a glucose oxidase-based method. This system was used over two 72-hour periods (on metformin alone [Week 0] and again after eight weeks of adjunctive DPP-4 inhibitor treatment [Week 8]) with glucose measurements every five minutes. The sensor was inserted on Day 0 and removed, after a 72-hour period, on Day 3. All analyses were conducted on data acquired on Days 1 and 2 to avoid distortion due to insertion or removal of the sensor and to avoid any bias due to a progressive deterioration in the reliability of the sensor readings. These data were averaged to generate 24-hour data. For valid analysis of a patient on a given day, CGM data had to be available for the entire 24-hour period. Patients were also asked to record six SMBG readings on each of these days to calibrate the CGM, and document important events (e.g. snacks and exercise).

2.4. Efficacy and safety assessments

CGM data were treated as detailed by Rodbard [29]. All CGM recordings were analyzed in a blinded fashion at a central core laboratory to evaluate changes between baseline and Week 8 on the two gliptins on the main efficacy endpoints pertaining to glycaemic variability and circadian control. Investigators and patients were also kept blinded to CGM recordings throughout the study. Daily glycaemic variability was assessed by the change in the mean amplitude of glucose excursions (MAGE) index, and through the standard deviation (SD) of the mean 24-hour blood glucose concentration. Day-to-day variability was assessed through the mean of daily differences (MoDD in mg/dL). In parallel, daily glycaemic control was assessed by the mean (M) daily CGM value, as well as by the times (in minutes/day) spent in optimal glycaemic range (70-140 mg/dL) and above predefined hyperglycaemic thresholds (140 and 180 mg/dL) together with the corresponding area under the curve (AUC) values. Hypoglycaemia was defined as at least two consecutive CGM readings of < 70 mg/dL.

2.5. Statistical analyses

Continuous variables are described by mean and standard deviation (SD) and in some cases median and range, and qualitative variables by frequency.

The primary analysis was conducted on the Per Protocol (PP) population. For consistency, all efficacy analyses were repeated in the ITT population which comprised all patients who received at least one dose of study medication and in whom both CGM recordings were successful. The PP population consisted of all ITT patients without a major protocol violation (reasons for exclusion were use of a disallowed concomitant medication in the form of parenteral corticosteroids, and poor compliance with the study treatment). Primary and secondary endpoint changes from baseline were compared between groups by analysis of covariance (ANCOVA), with treatment as classification variable and baseline value as covariate. AEs were reported in the safety population, which consisted of all patients who received at least one dose of study medication and who had at least one postbaseline safety assessment.

The statistical significance of changes from baseline was assessed within groups by Wilcoxon signed-rank tests for continuous variables and all tests were adjusted with a significance level of 5%. Statistical analyses were performed using SAS 8.2 software (SAS Institute, Cary, North Carolina, USA).
For this pilot study, sample size was essentially set on the basis of practical considerations and patient availability. In the only prior cross-sectional study with a similar CGM end point, an overall sample of 38 patients was big enough to show a significant difference in MAGE index between two treatment groups [31].

2.6. Ethics

The study was conducted according to the ethical principles of the declaration of Helsinki. The study and any amendments were approved by an Independent Ethics Committee and informed consent was obtained from each subject in writing before inclusion.

3. Results

3.1. Patient disposition, demographics and baseline characteristics

Seven centres selected 50 patients of whom 38 (19 in the vildagliptin group and 19 in the sitagliptin group) were randomised. One patient in the vildagliptin group withdrew consent and two in the sitagliptin group discontinued the study because of an AE, so 35 patients completed the study (92.1%). Of these 35 who completed the full eight weeks of treatment, the protocol was violated in three vildagliptin patients (use of parenteral corticosteroids and non compliance with treatment) and one CGM recording was not interpretable in each patient group, so 14 patients in the vildagliptin group and 16 in the sitagliptin group were included in the PP analysis.

Patient characteristics are shown for the randomised population (Supplementary data, Table S1). All study populations showed similar profiles and demographic characteristics were well balanced between the two groups. There were more men in both groups, mean age was 56.3 and the diabetes was relatively well-controlled with a mean baseline HbA1c of 7.1%. The history of T2DM, duration of metformin use and mean metformin dosage at randomization were also comparable between the two groups. About one-third of patients had at least one micro- or macrovascular diabetic complication and most patients (87%) presented other cardiovascular (CV) risk factors. Most patients were obese (mean BMI 31.8 kg/m² with 18% of the patients morbidly obese), 13% were smokers, 58% had hypertension and 58% dyslipidemia. Nearly 90% of patients were on at least one medication, mainly antihypertensive agents – ACE inhibitors (43%), angiotensin II receptor antagonists and beta-blockers (22–24%), either alone or in combination with a diuretic – lipid lowering agents (47%, notably statins in 42%) and antiplatelet drugs (one-third of patients).

3.2. Primary endpoint: CGM data on glucose variability and control

Mean glucose profiles over the two CGM recording periods – on metformin alone and after 8 weeks of adjunctive treatment with a DPP-4 inhibitor – are shown in Fig. 1A (vildagliptin) and B (sitagliptin).

Analysis of 24-hour variability as reflected by MAGE Index (Table 1) shows significant improvement versus baseline on metformin alone in both groups of about 15 mg/dL with no significant difference between the two DPP-4 inhibitors. Similarly, no significant difference between the two arms was observed in another measurement of daily variability, namely the SD in mean 24-hour CGM blood glucose readings. Neither gliptin induced any significant improvement in variability between different days as reflected by MoDD analysis.

Even in this relatively well-controlled population, both vildagliptin and sitagliptin enhanced daily glucose control over baseline on metformin alone, as measured by a range of CGM-based parameters (Fig. 1A and B, Supplementary data, Table S2). A series of analyses shows that vildagliptin consistently induced greater improvement in circadian glucose control, confirming the picture that emerges from the mean CGM curves (Fig. 1A and B). Vildagliptin induced a significant decrease in mean daily glycaemia (M) from a baseline of ~131 mg/dL, whereas sitagliptin did not from a similar baseline, with borderline significance in the Ancova superiority test of the between-group adjusted mean change from baseline (P = 0.07) (Table 1). Similarly, vildagliptin but not sitagliptin

![Fig. 1. Mean glycaemic profiles in the Per Protocol PP population at baseline on metformin alone (grey line) and after 8 weeks of the addition of gliptin treatment (black line). (A) vildagliptin (B) sitagliptin.](image-url)
Circadian glycaemic control at baseline and after 8 weeks of adjunctive vildagliptin or sitagliptin treatment, continuous blood glucose monitoring system (CGM) measurements, Per Protocol population.

### Glycemic variability

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<tr>
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<th>Vildagliptin</th>
<th>Sitagliptin</th>
<th>P change vilda vs. sita&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td></td>
<td>n</td>
<td>Mean ± SD</td>
<td>P vs. baseline</td>
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<tr>
<td>Mean amplitude of glucose excursions (MAGE) (mg/dL)</td>
<td>Baseline 14</td>
<td>67.0 ± 21.3</td>
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<td></td>
<td>Week 8 14</td>
<td>52.6 ± 16.4</td>
<td>0.03</td>
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<td>Standard deviation of mean 24-hour CGMS blood glucose readings (mg/dL)</td>
<td>Baseline 14</td>
<td>29.3 ± 8.0</td>
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<td></td>
<td>Week 8 14</td>
<td>24.2 ± 6.0</td>
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<td>Mean of daily differences (MoDD)</td>
<td>Baseline 14</td>
<td>27.9 ± 13.9</td>
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<td></td>
<td>Week 8 14</td>
<td>22.1 ± 4.9</td>
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### Glycemic control

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<th>Vildagliptin</th>
<th>Sitagliptin</th>
<th>P vs. baseline</th>
<th>P change vilda vs. sita&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
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<tr>
<td>Mean 24-hour blood glucose reading (M) (mg/dL) mean (± SD)</td>
<td>Baseline 14</td>
<td>130.6 ± 12.0</td>
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<td></td>
<td>Week 8 14</td>
<td>118.5 ± 12.5</td>
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<td>Time (min) spent in ideal range (70–140 mg/dL) mean (± SD)</td>
<td>Baseline 14</td>
<td>917 ± 167</td>
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<td>Week 8 14</td>
<td>1139 ± 231</td>
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<td>AUC ideal range (70–140 mg/dL) (mg/dL*h) mean (± SD)</td>
<td>Baseline 14</td>
<td>1255 ± 187</td>
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<td></td>
<td>Week 8 14</td>
<td>1038 ± 223</td>
<td>0.02</td>
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<td>Time spent above 140 mg/dL per day (min) mean (± SD)</td>
<td>Baseline 14</td>
<td>501 ± 179</td>
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<td></td>
<td>Week 8 14</td>
<td>273 ± 242</td>
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<td>AUC &gt; 140 mg/dL per day (mg/dL*h) mean (± SD)</td>
<td>Baseline 14</td>
<td>208 ± 115</td>
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<td></td>
<td>Week 8 14</td>
<td>103 ± 120</td>
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<td>Time above 180 mg/dL per day (min) mean (± SD)</td>
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<td>120 ± 90</td>
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<td></td>
<td>Week 8 14</td>
<td>51 ± 73</td>
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<td>Peak 24-hour glycaemia reading (mg/dL) mean (± SD)</td>
<td>Baseline 14</td>
<td>201 ± 16</td>
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<td></td>
<td>Week 8 14</td>
<td>182 ± 29</td>
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<td>Minimum blood glucose reading during the night (mg/dL) mean (± SD)</td>
<td>Baseline 14</td>
<td>95 ± 20</td>
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<td>Week 8 14</td>
<td>84 ± 16</td>
<td>0.15</td>
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<td>Postprandial Hyperglycaemia&lt;sup&gt;b&lt;/sup&gt; AUCpp (mg/dL*h) mean (± SD)</td>
<td>Baseline 14</td>
<td>443 ± 133</td>
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<td></td>
<td>Week 8 14</td>
<td>294 ± 127</td>
<td>&lt;0.01</td>
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<tr>
<td>Overall Hyperglycaemia AUCtotal (mg/dL*h) mean (± SD)</td>
<td>Baseline 14</td>
<td>795 ± 227</td>
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<td></td>
<td>Week 8 14</td>
<td>504 ± 274</td>
<td>0.01</td>
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<tr>
<td>Basal Hyperglycaemia AUCb (= AUCtotal–AUCpp) (mg/dL*h) mean (± SD)</td>
<td>Baseline 14</td>
<td>352 ± 175</td>
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<td></td>
<td>Week 8 14</td>
<td>209 ± 198</td>
<td>0.04</td>
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_P versus baseline; Wilcoxon test._

<sup>a</sup> Difference in adjusted mean change between groups from Ancova model.

<sup>b</sup> All three 4-hour postprandial periods throughout the day.

Induced significant improvements from baseline in both the time spent within the ideal glycaemic range (70–140 mg/dL) and the corresponding AUC (Ancova superiority test of the between-group adjusted mean change from baseline, _P_ = 0.02). These differences are paralleled in all results for time spent in hyperglycaemia above the two predefined threshold glucose concentrations that were analyzed (140 and 180 mg/dL): vildagliptin almost halved the time spent in the hyperglycaemic range over 140 mg/dL (−46%, _P_ = 0.02) while sitagliptin reduced it by −12% ( _P_ = 0.46). All corresponding AUC results (which reflect not only time but also amplitude) show the same trends. Furthermore, while both vildagliptin and sitagliptin induced significant decreases in postprandial hyperglycaemia (AUCpp), only vildagliptin had an impact on overall glycaemic exposure (AUCtotal), namely a reduction of 37% ( _P_ = 0.01) compared with a reduction of 9% ( _P_ = 0.5) on sitagliptin (Ancova superiority test _P_ = 0.07). In parallel, a significant decrease was seen in basal hyperglycaemia (AUCb) on vildagliptin (from 352 down to 209 mg/dL*h) as opposed to a small increase on sitagliptin (from 349 up to 381 mg/dL*h) (Table 1 and Fig. 2). Similarly, the mean
CGM traces (Fig. 1) suggest that the main difference between the two treatment groups is seen overnight, between midnight and 6 am, while the magnitude of the decrease in the peak following breakfast is fairly similar. Consistent with the decrease seen during the overnight period, vildagliptin induced a decrease in the minimum blood glucose reading during the night, but which was still well above the thresholds for hypoglycaemia.

All the analyses shown correspond to the PP population and results were consistent in the ITT population.

3.3. Secondary endpoints: usual blood glucose control parameters

With reference to the laboratory parameters classically used to evaluate the efficacy of treatment (Supplementary data, Table. S2), vildagliptin significantly brought down HbA1c: the mean change from baseline was –0.5% in the vildagliptin group [P < 0.01] compared with –0.3% in the sitagliptin group [NS], with the difference between the two treatment groups insignificant. FPG was reduced in both, while the mean of the six SMBG readings was only significantly reduced in the vildagliptin group [-12 mg/dL; P < 0.01] (Supplementary data, Table. S2).

3.4. Safety

Few episodes of symptomatic hypoglycaemia were reported as AEs (two in each group, suspected in one vildagliptin patient and two sitagliptin patients, none severe and none leading to discontinuation). With CGM, no differences emerged in either the time spent with a glucose concentration of less than 70 mg/dL or the incidence of hypoglycaemia (two successive readings below 70 mg/dL), neither between the two treatment arms nor after the addition of a DPP-4 inhibitor compared with baseline on metformin alone. The baseline CGM data showed hypoglycaemia in 10 patients (33%) on metformin alone and this persisted after the addition of a DPP4 inhibitor (in 12 patients [40%] with no significant between-group difference: seven patients in the vildagliptin group and five in the sitagliptin group).

A summary of all AEs is presented in (Supplementary data, Table. S3). The only AE which was classified as serious concerned a severe case of toothache requiring hospitalization (in the sitagliptin group). Two patients discontinued because of AEs: one case of severe nausea, headache and muscle spasm, and one case of headache. Both of these AEs were suspected of being related to the study treatment and occurred in the sitagliptin group. No AE leading to discontinuation occurred in the vildagliptin group.

Mean weight did not vary by more than one kilogram in the course of the study.

4. Discussion

This study, conducted in T2DM patients with only moderately uncontrolled disease, was the first randomized, head-to-head trial to study glycaemic profiles on vildagliptin and sitagliptin, as measured using 24-hour CGM data. While both DPP-4 inhibitors improved glucose tolerance and variability, circadian profiles were better on vildagliptin and this was most evident overnight. Both DPP-4 inhibitors effectively attenuated 24-hour glycaemic variability as measured by MAGE index and SD of the mean blood glucose concentration. Reductions in MAGE were correlated to baseline readings and, on average, a drop of 15 mg/dL was observed, even in this population with relatively well-controlled HbA1c at the outset. This is consistent with the findings of a recent short-term, open-label pilot study which showed a decrease of MAGE (strongly related to baseline levels), SD and average 24-hour blood glucose level after just two days of sitagliptin treatment [6].

Parallel analysis of a series of predefined parameters related to daily glucose control and glycaemic exposure showed that significant improvements from baseline were only observed in the vildagliptin group. Vildagliptin added 222 minutes (15% of 24-hours; P = 0.02) to the mean time patients spent at a satisfactory glucose concentration (70–140 mg/dL), whereas sitagliptin added 85 minutes (6% of 24 hours) (P = 0.33); moreover, vildagliptin induced significant drops in hyperglycaemia (considering thresholds of both 140 and 180 mg/dL) while sitagliptin did not. All these effects are apparent from both the “time spent” analyses of the CGM data and the corresponding AUC values (although the latter are more clinically informative since they integrate information on the magnitude of the fluctuations as well as time). Both vildagliptin and sitagliptin induced significant decreases in postprandial hyperglycaemia, but only vildagliptin had a significant effect on overall hyperglycaemia (reduced by 37%; P = 0.01) and, similarly, only vildagliptin induced a reduction in the mean 24-h blood glucose concentration (−12 mg/dL; P = 0.01). Taking these observations together, it would seem that the greater circadian efficacy of vildagliptin over sitagliptin would be predominantly due to a stronger effect on basal hyperglycaemia (which was indeed significantly reduced by 41%, while unchanged with sitagliptin), notably as a result of improved glucose control between midnight and 6 am. The consistency of the results for different, related parameters and in both analysis populations (PP and ITT) points up the solidity of these observations. It could be hypothesized that the effect seen with vildagliptin on basal hyperglycaemia could be due to prolonged elevation of intact GLP-1 overnight. Raised intact GLP-1 levels have been...
consistently observed with vildagliptin not only after meal ingestion but also in the fasting state [13–16] probably as a result of sustained blocking of the active site of DPP-4 [12]. This would maintain a prolonged suppression of glucagon and hepatic glucose production overnight, thus lowering hyperglycaemia during this period [14,16,31,32].

These high-resolution CGM results are not contradicted by data from conventional laboratory testing, i.e. the mean change from baseline in HbA1c (–0.5% in the vildagliptin group [P < 0.01] and –0.3% in the sitagliptin group [NS]), although no significant difference was observed between the two treatment groups, which is to be expected with a small sample size and relatively short duration.

Neither gliptin induced an increase in the frequency of episodes of hypoglycaemia versus baseline on metformin (either symptomatic hypoglycaemia reported as AEs or episodes diagnosed by CGM), which is a key consideration in the decision to target tighter glycaemic control [33].

Thus, both vildagliptin and sitagliptin helped lower blood glucose concentration when combined with metformin and effectively attenuated glucose variability, while only vildagliptin induced a significant decrease on overall hyperglycaemia, mainly driven by reduction on basal hyperglycaemia. The main findings of this study already clearly emerge in a small group of patients in whom a metformin regimen based on an optimal dosage was still achieving some good degree of control (7.1% at baseline). This points up the benefit of early addition of a DPP-4 inhibitor to metformin without waiting for glucose control to further deteriorate while not exposing patients to an increased risk of hypoglycaemia [33,34]. Acute glucose fluctuations have been shown to correlate with markers of oxidative stress which may exacerbate vascular complications of diabetes [8,35,36] and stabilization of glucose concentration over the 24 hour cycle could be expected to be beneficial [9]. Since such acute fluctuations could be present even in moderately well-controlled T2DM patients [37], the early addition of a DPP-4 inhibitor to metformin might be of interest and CGM would be a valuable tool to guide this therapeutic decision. A corollary benefit of CGM is that it has been shown to convince patients of the concrete advantages of compliance with recommended lifestyle measures [38,39].

It is important to take into account the limitations and strengths of our work. The main limitation of this small pilot study, the first head-to-head comparison of glycaemic profiles on two DPP-4 inhibitors, is its limited sample size and relatively short duration of only 8 weeks. However, a number of factors support the robustness of the results: randomization was centralized; the PROBE methodology ensured reliable, objective results for the main efficacy end points addressed in the study (with all CGM data blinded and analyzed centrally at a core laboratory); and a series of closely related parameters showed consistent results in the two treatment groups.

In conclusion, the results of this pilot study suggest that vildagliptin affords better circadian glucose control than sitagliptin, as add-on to metformin in moderately controlled T2DM patients. Larger-scale studies will be required to confirm this.

Contributions

Professor Guerci was the principal investigator, contributed to the initial data interpretation and overall clinical interpretation, and was involved in drafting the manuscript. Professor Monnier contributed to study design and methodology, and was a key contributor in data interpretation and drafting the manuscript. Professors Valensi, Huet and Raccah and doctors Petit and Serusclat represented the study investigators and contributed to the clinical interpretation of the data. Dr. Colette was responsible for the blinded analysis of the CGMS data at the core lab and contributed to study design and data interpretation. S. Quere was responsible for the statistical analysis. Dr. Dejager was critical to study design and conduct, initial data interpretation, and drafting the manuscript. All authors were involved in manuscript revisions and are responsible for intellectual content.

Disclosure of interest

Pr. B.Guerci has received fees for consultancy, advisory boards, speaking, travel or accommodation from GlaxoSmithKline, Eli Lilly, Merck Sharpe and Dohme, AstraZeneca, Bristol Myers Squibb, Pfizer, Novo Nordisk, Sanofi-Aventis, Novartis, Abbott, Lifescan, Medtronic and Menarini. Pr. L Monnier and Dr. C Colette declare no conflict of interest with the content of this article and did not received any additional support from Novartis Pharma than those related to the development of this paper. Dr. P. Serusclat has received funding for research and consulting/speaking for Novartis, as well as from other manufacturers of drugs in this class including Merck Sharpe and Dohme, AstraZeneca and Bristol Myers Squibb. Pr. P. Valensi has received fees for consultancy, advisory boards, speaking or research grants from Merck Santé, GlaxoSmithKline, Merck Sharp Dohme, Novo Nordisk, Bayer, Abbott, Novartis, Pierre Fabre, Abbott, Eli-Lilly, Bayer, Bristol Myers Squib – AstraZeneca, Boehringer Ingelheim. Pr D. Raccah has received honoraria for lectures and advisory boards from Sanofi-Aventis, Novo Nordisk, Lilly, Merck Serono, GlaxoSmithKline, Novartis, Roche and Merck Sharp and Dohme. Stephane Quéré and Sylvie Dejager are employees of Novartis Pharmaceuticals.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jdiab.2012.06.001.
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