Effect of Renal Insufficiency on the Pharmacokinetics of Sitagliptin, a Dipeptidyl Peptidase-4 Inhibitor

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Running title: Kinetics of Sitagliptin in Renal Insufficiency

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Sitagliptin is an oral, once-daily, potent, and highly selective dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes (1). In subjects with normal renal function (creatinine clearance (CrCl) >80mL/min), 75 to 80% of an oral dose was excreted unchanged in urine. Renal clearance was approximately 350mL/min indicating that active secretion of sitagliptin rather than only filtration is involved in renal excretion. Thus, renal excretion is the primary mechanism of elimination for sitagliptin (2). The purpose of this study was to evaluate the pharmacokinetics (PK) of single doses of sitagliptin in patients with various degrees of renal insufficiency (RI).

Research Design and Methods

This was an open-label, 2-part study (Sitagliptin Protocol 008, ClinicalTrials.gov; NCT00418366) in 30 otherwise healthy, males and females (18-75 years of age), with a body mass index (BMI) ≤40kg/m². Subjects were assigned to one of 5 groups (n=6/group) based on the following criterion for degree of RI: mild (CrCl 50-80mL/min); moderate (CrCl 30-50mL/min); severe (CrCl <30mL/min); end-stage renal disease (ESRD) on hemodialysis; and normal (CrCl >80mL/min). Healthy subjects (n = 145) from 11 other studies were included in a historical control group to supplement those studied here. CrCl values were based on measured 24-hour urinary creatinine excretion (this study) or calculated using the Cockroft-Gault formula (historical controls).

Since sitagliptin plasma concentrations were expected to increase with RI, a 50-mg dose was expected to be well-tolerated in the event of substantial increases in drug concentrations.

All subjects provided written informed consent. The protocol was approved by investigational review boards, and carried out in accordance with the principles of the Declaration of Helsinki.

In Part I, 18 patients with mild to severe RI, and 6 healthy concurrent control subjects received a single 50-mg dose of sitagliptin, followed by 96 hours of plasma sampling and 48 hours for urine collection for sitagliptin concentrations. During Period 1 of Part II, patients with ESRD requiring hemodialysis received a single 50-mg dose of sitagliptin 48 hours prior to their normally scheduled hemodialysis session. Following Period 1 and at least a one-week wash-off, the same ESRD patients received a single 50-mg sitagliptin dose 4 hours prior to their hemodialysis session to quantify the amount of sitagliptin removed by dialysis. Plasma and dialysate samples were collected at prespecified times up to 96 hours following dosing.

Pharmacokinetic Analysis

Sitagliptin was measured in plasma, urine and dialysate samples by MS/MS detection following specialized HPLC chromatography with an internal standard (3). Calculations for PK parameters were completed according to established methods (4,5). The area under the sitagliptin plasma concentration curve from time zero extrapolated to infinity (AUC$_{0-\infty}$) was considered the most relevant pharmacokinetic parameter since it provides an estimate of the plasma drug exposure at steady state.

Safety

Safety and tolerability were assessed from adverse experiences and measurements of vital signs, 12-lead ECGs and laboratory safety parameters. Adverse experiences were evaluated as to their intensity, seriousness, and relationship to study drug.
**Statistical Analyses**

Since sitagliptin AUC\(_{0-\infty}\) had been shown to be dose-proportional following single oral doses from 25 to 800 mg (2,5), AUC\(_{0-\infty}\) values for healthy subjects from clinical studies were adjusted based on a 50-mg dose and since these results were similar to the 6 concurrent controls, these data were pooled for the analysis. Historical data for other PK parameters were limited to those from a 50-mg dose group (see table). ANCOVA models containing CrCl as a continuous variable or as a categorical variable and covariates of age, gender and weight were both used for analysis of PK parameter data. Based on the apparent wide therapeutic index of sitagliptin (2,5,6), an increase in plasma sitagliptin exposure (i.e., AUC\(_{0-\infty}\)) of less than 2-fold was not considered clinically meaningful.

**Results**

All patients completed the study. Using the continuous model, increases in sitagliptin AUC\(_{0-\infty}\) were <2-fold for mild RI patients relative to the normal renal function controls (Table). From the categorical analysis, increases in sitagliptin AUC\(_{0-\infty}\) were approximately 2.3-fold higher for moderate RI patients. Increases in sitagliptin AUC\(_{0-\infty}\) were approximately 3.8-fold higher for severe RI. Increases in sitagliptin AUC\(_{0-\infty}\) were approximately 4.5-fold higher for patients with ESRD. \(C_{\text{max}}\) was moderately increased and \(C_{24}\) was increased as renal function decreased. \(T_{\text{max}}\) was significantly increased in patients with ESRD, and the terminal \(t_{1/2}\) was increased with decreasing renal function. Renal clearance of sitagliptin was approximately proportional to CrCl.

The fraction of dose removed by dialysis was small with 13.5% and 3.5% for hemodialysis initiated at 4 and 48 hours postdose, respectively. Plasma protein binding was not altered in uremic plasma from the RI patients (median 36%, range 33 to 40%) as compared to that from concurrent controls (median 37%, range 34 to 43%). Single doses of sitagliptin were well-tolerated in this study.

**Conclusions**

Based on the present findings, sitagliptin dose adjustments are recommended for patients with moderate or severe RI or ESRD in order to provide plasma sitagliptin exposure comparable to patients with normal renal function. The recommended sitagliptin dosage adjustments are as follows: no adjustment for patients with mild RI (CrCl = 50-80mL/min); a 2-fold decrease in the clinical dose of 100 mg q.d. (i.e., 50 mg q.d.) for patients with moderate RI (CrCl = 30-50mL/min) (~serum Cr levels [mg/dL] >1.7 and ≤3.0 [men]; >1.5 and ≤2.5 [women]); and a 4-fold decrease in the clinical dose (25mg q.d.) for patients with severe RI (CrCl <30mL/min ) or ESRD (~serum Cr levels [mg/dL] >3.0 [men]; >2.5 [women]; or on dialysis). Moreover, since hemodialysis removed sitagliptin to a modest extent, sitagliptin can be administered without respect to the timing of hemodialysis in patients with ESRD.

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References


### Table. Summary Statistics of Sitagliptin Pharmacokinetic Parameters Following Administration of Single Oral Doses of 50 mg Sitagliptin in Patients with Varying Degrees of Renal Function and Healthy Subjects with Normal Renal Function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pooled Normal (N=58-151)</th>
<th>Mild (N=6)</th>
<th>Moderate (N=6)</th>
<th>Severe (N=6)</th>
<th>ESRD† (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean‡</td>
<td>Mean ‡</td>
<td>GMR§ (90% CI)</td>
<td>Mean ‡</td>
<td>GMR§ (90% CI)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;, µM·hr</td>
<td>4.40</td>
<td>7.09</td>
<td>1.61</td>
<td>9.96</td>
<td>2.26</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, nM</td>
<td>391</td>
<td>527</td>
<td>1.35</td>
<td>560</td>
<td>1.43</td>
</tr>
<tr>
<td>C&lt;sub&gt;24hr&lt;/sub&gt;, nM</td>
<td>43.7</td>
<td>83.3</td>
<td>1.91</td>
<td>129</td>
<td>2.96</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;, hr</td>
<td>3.0</td>
<td>3.0</td>
<td>p=0.303</td>
<td>3.0</td>
<td>P=0.771</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;, hr**</td>
<td>13.1</td>
<td>16.1</td>
<td>p=0.011</td>
<td>19.1</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>f&lt;sub&gt;0-∞&lt;/sub&gt;††</td>
<td>0.76</td>
<td>0.84</td>
<td>0.09</td>
<td>0.64</td>
<td>-0.12</td>
</tr>
<tr>
<td>Cl&lt;sub&gt;R&lt;/sub&gt;, ‡‡ mL/min</td>
<td>339</td>
<td>242</td>
<td>0.71</td>
<td>126</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Sample size for AUC<sub>0-∞</sub> was 151 and 58 for f<sub>0-∞</sub> and Cl<sub>R</sub> and 82 for all the rest. Healthy control data included data from various Phase I safety/pharmacokinetic/pharmacodynamic protocols; Mean values for normal subjects from protocol 008 included in pooled sample of normal subjects: AUC<sub>0-∞</sub> 4.59, C<sub>max</sub> 347, C<sub>24hr</sub> 49.5, T<sub>max</sub> 4.5, t<sub>1/2</sub> 15.1, f<sub>0-∞</sub> 0.76 and Cl<sub>R</sub> 341

† Hemodialysis at 48 hours postdose in subjects with ESRD (end-stage renal disease)
‡ Geometric least-squares mean for AUC<sub>0-∞</sub>, C<sub>max</sub>, C<sub>24hr</sub>, and Cl<sub>R</sub>; median for T<sub>max</sub>; harmonic mean for t<sub>1/2</sub>; arithmetic mean for f<sub>0-∞</sub>
§ GMR = Geometric Mean Ratio; CI = Confidence Interval; p-values reported for T<sub>max</sub> and t<sub>1/2</sub>; Arithmetic mean difference and 90% confidence intervals reported for f<sub>0-∞</sub>
‖ AUC<sub>0-∞</sub> = Area under the plasma level vs. time curve from time zero extrapolated to infinity from the last measured time point and dose-adjusted to 50 mg (single oral doses of 25, 50, 100, 200, 400, 600 and 800 mg)
¶ Fraction of dose excreted unchanged in urine extrapolated to infinity
** C<sub>24hr</sub> = concentration at 24 hr;
*** Terminal t<sub>1/2</sub>
†† C<sub>max</sub> = highest concentration observed
‡‡ Renal Clearance
NA = not applicable; urine was not collected from subjects with ESRD