A Phase 1, Open-Label Evaluation of the Pharmacokinetics and Safety of a Single Dose of Apraglutide in Subjects with Normal and Impaired Renal Function

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OBJECTIVE

• Patients with short bowel syndrome and intestinal failure (SBS-IF) have increased renal-related drug clearance.

• With currently available glucagon-like peptide 2 (GLP-2) therapy, teduglutide, dosage reductions are recommended for patients with moderate and severe renal impairment and end-stage renal disease.

• Apraglutide has unique pharmacokinetic (PK) and pharmacodynamic (PD) properties resulting in a longer-half life than subcutaneously injected native GLP-2 or other GLP-2 analogs.

• Results of preclinical studies indicated apraglutide to have:
  - Slow absorption
  - High protein binding
  - Resistance to dipeptidyl-peptide-4 (DPP4) cleavage
  - Low clearance.

• Apraglutide is degraded into small peptides and amino acids via catabolic pathways, similar to endogenous GLP-2.

• Previous preclinical studies and clinical trials showed no intact parent compound (apraglutide) present in urine, suggesting renal elimination does not play a significant role in apraglutide clearance.

METHODS

• Two-stage, open label, multi-center, non-randomized trial.

• Renal function was calculated by the estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology (CKD-EPI) creatinine equation.

• Part 1 of clinical trial (if applicable): To assess the PK of apraglutide in subjects with normal renal function following single subcutaneous (SC) dose administration.

• Part 2 of clinical trial (if applicable): To assess the PK of apraglutide in subjects with moderate and mild renal impairment compared to matched control subjects following single SC dose administration.

Secondary Objective

• To assess the safety and tolerability of apraglutide administered to subjects with varying degrees of impaired renal function.

RESULTS

Demographics

• Eight subjects with severe renal impairment and 8 subjects with normal renal function were enrolled and completed the study.

• The two cohorts were well matched.

Table 1. Demographic Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Severe Renal Impairment</th>
<th>Normal Renal Function</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>77.2 (70-96.6)</td>
<td>97.9 (92.6-103.4)</td>
<td>0.4078</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.9 (164.5-176.5)</td>
<td>174.9 (161.5-180.1)</td>
<td>0.2304</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.4 (24.1-24.7)</td>
<td>24.8 (24.5-25.1)</td>
<td>0.0985</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 (54.7-67)</td>
<td>61 (59.0-69.1)</td>
<td>0.1161</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>21.6 (7.7-38.8)</td>
<td>97.6 (86.7-108.3)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Safety

• Five of the 16 total subjects reported 10 adverse events (AEs); all had resolved at the end of study visit.

- 5 mild-severity AEs and 5 moderate-severity AEs

- 5 treatment-related AEs, all were reported by subjects with severe renal impairment. These treatment-related AEs do not differ from those reported to date in other apraglutide clinical studies.

- 1 AE: mild-severity anaphylaxis, severe enough to require treatment with epinephrine.

- 2 AEs: moderate-severity nausea and emesis

- 1 AE: mild-severity erythematous papule

- 1 AE: mild-severity ecchymosis at the injection site

• No serious adverse event (SAE) or death was reported.

• No discontinuations occurred.

• No clinically relevant changes within cohort or differences between cohorts were observed over time in clinical chemistry, hematology, urinalysis, or other safety parameters.

• No relevant changes in vital signs (blood pressure, heart rate, and body temperature) or electrocardiograms occurred from screening to follow-up.

Table 2. Summary of Adverse Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Any AE</th>
<th>Severe Renal Impairment</th>
<th>Normal Renal Function</th>
<th>Total N=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/events</td>
<td>3/7</td>
<td>1/2</td>
<td>2/5</td>
<td>5/10</td>
</tr>
<tr>
<td>Treatment-Related AEs</td>
<td>3/5</td>
<td>2/3</td>
<td>1/2</td>
<td>5/10</td>
</tr>
<tr>
<td>SAEs</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Discontinuations</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>

Pharmacokinetic

• The primary endpoint showed that apraglutide achieved a higher Cmax and AUC0inf in subjects with normal renal function vs. subjects with severely impaired renal function.

• The mean Cmax, and AUC0inf in the normal renal function cohort was due to one subject with the lowest body weight (76.2 kg), who had higher Cmax (153.6 ng/mL) and AUC0inf (12,349 h x ng/mL).

• Body weight is a known covariate on the apparent volume of distribution and clearance of apraglutide. Thus, apraglutide plasma AUC and Cmax increase with decreasing body weight independent of dose.

• This finding confirms that body weight is the major covariate of apraglutide PK.

• The point estimates and 90% CIs for the geometric least-square mean ratio of AUC0inf and Cmax met the criteria in order to not proceed to Part 2 of the study.

• The upper bound of the 90% CI for Cmax and AUC0inf was below 2, indicating that that renal impaired subjects did not risk unreasonably overexposure (double exposure) to apraglutide.

Table 3. Analysis of Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Renal Impairment</th>
<th>Renal Function</th>
<th>Mean Ratio 90%CI</th>
<th>90%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0inf (ng/mL)</td>
<td>3350</td>
<td>5050</td>
<td>0.694</td>
<td>0.458, 1.050</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>39.5</td>
<td>65.8</td>
<td>0.620</td>
<td>0.423, 0.908</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• Apraglutide is a novel long-acting synthetic GLP-2 analog rationally designed to optimize the PK profile.

• Due to high protein binding, renal elimination does not play a significant role in apraglutide clearance. This was supported by previous preclinical studies and clinical trials showing no intact parent compound (apraglutide) present in urine.

• Single dose of 5 mg apraglutide in subjects with severe renal disease and in healthy matched subjects was well-tolerated.

• There was no apraglutide overexposure in subjects with severe renal impairment compared to the healthy subjects.

• Results of this study are clinically significant. Since 28% of patients with SBS-IF have renal impairment and may not be candidates for treatment with currently available GLP-2, teduglutide, which requires dose adjustment.

• Apraglutide dose adjustments are not necessary for SBS-IF patients with renal impairment.

REFERENCES


AUTHORS DISCLOSURES

The study was sponsored by VectivBio. N. Hurley and N. Youssef are employees of the study sponsor. G. Gregl and E. Michel received fee for service as a consultants who designed and oversaw the conduct of the study.