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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Gerard Greig,[1] Niamh Hurley,[1] Eric Michel,[1] Nader Youssef[1]
[1]VectivBio, AG. Basel, Switzerland

Introduction

- Patients with short bowel syndrome and intestinal failure (SBS-IF) have an increased risk of complications, including renal dysfunction.[1]
- 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 and other GLP-2 analogs.
- Results of preclinical studies indicated apraglutide to have:
  - Slow absorption
  - High protein binding
  - Resistance to dipeptidyl peptidase-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.

OBJECTIVE

Primary Objective

- Part 1 of clinical trial: To assess the PK of apraglutide in subjects with severe renal impairment compared to matched control 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

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: 8 subjects with severe renal impairment (Cohort 1) and 8 subjects with normal renal function (Cohort 2) to ensure ≥6 evaluable subjects in each cohort. The severe renal impairment cohort were recruited first. Pooled demographics across the 8 enrolled severe impairment subjects were used to determine a mean for age and weight. Healthy subjects were recruited such that each subject's age was within ±10 years and weight was within ±15 kg of the mean of the severe renal impairment cohort.
- Part 2: According to plan, the study was stopped after completion of Part 1, because exposure of subjects with severe renal impairment was not greater than that of healthy subjects.

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

Parameter	Severe Renal Impairment	Normal Renal Function	p-value
Weight (kg)	90.1 (77.7-98.2)	86.7 (76.2-98.4)	0.4078
Height (cm)	171.9 (164.5-178.5)	174.9 (168.5-181.0)	0.2304
BMI (kg/m^2)	30.6 (24.4-33.7)	28.3 (25.8-31.5)	0.09856
Age (years)	66 (54-75)	60 (56-70)	0.1181
eGFR (mL/min/1.73m^2)	21.6 (11.4-30.0)	97.6 (91.4-112.3)	NA

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 alanine transaminase increase
  - 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, urine, 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

Parameter	Severe Renal Impairment N=8	Normal Renal Function N=8	Total N=16
	n / events		
Any AE	3 / 7	2 / 3	5 / 10
Treatment-Related AEs	3 / 5	0 / 0	3 / 5
SAEs	0 / 0	0 / 0	0 / 0
Discontinuations	0 / 0	0 / 0	0 / 0

Pharmacokinetic

- The primary endpoint showed that apraglutide achieved a higher C_{max} and AUC_{inf} in subjects with normal renal function vs. subjects with severely impaired renal function.
  - The higher mean C_{max} and AUC_{inf} in the normal renal function cohort was due to one subject with the lowest body weight (76.2 kg), who had higher C_{max} (153.6 ng/mL) and AUC_{inf} (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 C_{max} 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 AUC_{inf} and C_{max} met the criteria in order to not proceed to Part 2 of the study.
- The upper bound of the 90% CI for C_{max} and AUC_{inf} was below 2, indicating that that renal impaired subjects did not risk unreasonable overexposure (double exposure) to apraglutide.

Figure 1. Apraglutide Mean Concentrations by Cohorts

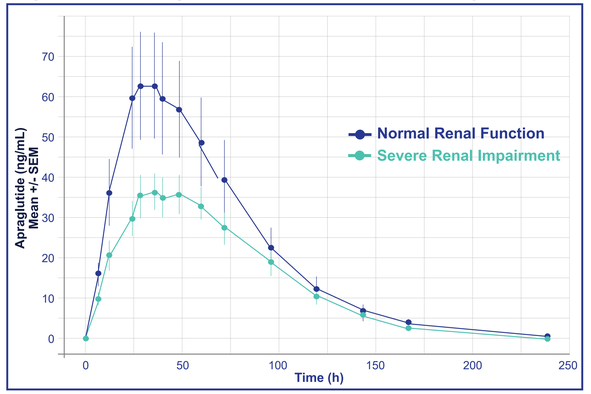

Table 3. Analysis of Pharmacokinetic Parameters

Parameter	Severe Renal Impairment	Normal Renal Function	Geometric Mean Ratio	90%CI
C_{max} (ng/mL)	39.5	65.8	0.620	0.423, 0.909
AUC_{inf} (h x ng/mL)	3330	5050	0.694	0.458, 1.050

AUC_{inf}, area under the curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed concentration

CONCLUSIONS

- **Apraglutide is a novel long-acting synthetic GLP-2 analog rationally designed to optimize the PK profile[1]**
- **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[2] 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

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AUTHORS DISCLOSURES

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