Protocol Number: TA799-014

Official Title: 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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Statistical Analysis Plan

Sponsor:	VectivBio AG
Protocol No:	TA799-014
Protocol Title:	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
PRA Project ID:	[redacted]
Version Date:	02-Nov-2020

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Sponsor Representative / Title:	[redacted]
Signature of Sponsor Representative / Date:	
Name of Author / Title:	
Signature of Author / Date:	

2.0 Table of Contents

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under VectivBio AG Protocol TA799-014.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol dated 11-Sep-2020 (including all amendments up to this protocol date) and the final eCRF(s) dated 21-Sep-2020.

An approved and signed SAP is a requirement for database lock. An approved SAP is also required for unblinding of the study treatments.

This SAP only covers the results that will be processed by the PRA Early Development Services (EDS) Biostatistics Department.

PRA EDS will perform the pharmacokinetic (PK), safety and tolerability evaluation.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

This is the first version of the SAP.

5.0 Study Objectives

5.1 Primary

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.

5.1.1 Primary Endpoint

Plasma apraglutide PK parameters: Cmax and AUCinf, AUClast, AUC0-7days, Tmax, λz, t½, CL/F, Vz/F. Cmax and AUCinf or AUClast as primary PK parameters. All others as secondary PK parameters.

5.2 Secondary

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

5.2.1 Secondary Endpoint

Adverse event (AE) (type, frequency and intensity), AE of Special Interest (AESIs), vital signs (systolic and diastolic blood pressure (BP), heart rate), recorded triplicate electrocardiogram (ECG) (intervals, rhythm, and morphology), clinical chemistry, hematology, and urinalysis.

6.0 Study Design

This is a Phase 1, non-randomized, open-label, single-dose trial to evaluate the effect of varying degrees of impaired renal function on the PK, safety, and tolerability of apraglutide administered to trial subjects by SC injection in a clinical research unit (CRU). A staged approach, as outlined below, will be followed in the trial. Subjects will be selected and categorized into normal renal function or renal impairment groups based

on their estimated glomerular filtration rate (eGFR) which will be calculated using the Chronic Kidney Disease Epidemiology (CKD-EPI) Creatinine Equation (Table 1).

Table 1: CKD-EPI Equation

Part 1

Cohort[a]	eGFR (mL/min/1.73 m^2)[b]	N
1 (Severe Renal Impairment)	<30 not on hemodialysis	8
2 (Normal Healthy Match)	≥90	8

Part 2

Cohort[a]	eGFR (mL/min/1.73 m^2)[b]	N
3 (Moderate Renal Impairment)	≥30 to <60	8
4 (Mild Renal Impairment)	≥60 and<90	8

a. Stages of Renal Impairment are based on the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Chronic Kidney Disease (CKD).

b. Estimated glomerular filtration rate (eGFR) based on Chronic Kidney Disease Epidemiology (CKD-EPI). The baseline eGFR will be obtained by taking the mean of the eGFR obtained from screening and from historical values within a 3-month period from screening. If no historical measurement is available, a second baseline eGFR sample will be taken during the screening period (≥72 hours apart, but no more than 14 days apart) and the mean of the two values will be used for the group assignment; the second baseline eGFR sample may be obtained at the time of check-in. Subjects will be assigned to one of the 4 renal function groups based on eGFR values at screening. Estimated GFR will be calculated using the CKD-EPI Creatinine Equation:
$eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]
Notes: eGFR is expressed as mL/min/1.73 m^2 of body surface area, SCr (serum creatinine) is expressed in mg/dL
κ = 0.7 (females) or 0.9 (males)
α = -0.329 (females) or -0.411 (males)
min = indicates the minimum of SCr/κ or 1
max = indicates the maximum of SCr/κ or 1
age is in years

Reasonable efforts will be made to enroll at least two subjects with eGFR values of <20 mL/min/1.73 m^2

Part 1 of clinical trial: A total of approximately 16 subjects will be enrolled in Part 1: approximately eight subjects with severe renal impairment (Cohort 1) and approximately eight subjects with normal renal function (Cohort 2) to ensure at least six evaluable subjects in each group. Subjects from the severe renal impairment group will be recruited first. The demographics will be pooled across enrolled subjects to determine an average value for age and weight in the severe impairment group. Subsequently, the healthy subjects will be recruited later such that each subject's age is within ±10 years and weight is within ±15 kg of the mean of the severe renal impairment group. Attempts will be made to maintain a similar male/female ratio composition between groups. Care will be taken when recruiting the healthy subjects such that the entire group is not of substantially different age or of substantially different body weight than the severely renally impaired subjects.

Criteria to proceed to Part 2: After evaluation from Part 1, Part 2 will be conducted if the point estimate of apraglutide area under the concentration-time curve from time 0 to infinity (AUCinf, or to the time of the last quantifiable concentration (AUClast), if AUCinf cannot be calculated) geometric mean ratio (GMR) for the severe renal impairment group compared to the control group (normal renal function group) is ≥2.

If criterion is not met, the trial will stop after Part 1. If there are subjects who withdraw or discontinue treatment from the normal or severe renal impairment groups and who are considered to be non-evaluable with respect to the primary PK objective, replacement subjects can be enrolled at the discretion of the sponsor.

Part 2 of clinical trial: If the decision criterion to proceed to Part 2 is met, approximately eight subjects each with moderate (Cohort 3) and mild (Cohort 4) renal impairment will be enrolled to ensure at least six

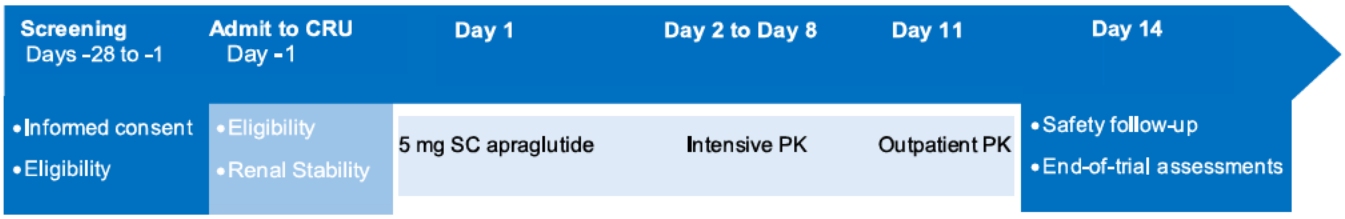
evaluable subjects in each group. As in Part 1, renal impairment classification will be based on eGFR. Healthy subjects will not be enrolled in Part 2. Healthy subjects from Part 1 will be used as the control group of the moderate and mild renal impairment subjects.

When recruiting the Part 2 subjects, attempts to match the entire group to the subjects in Part 1 with respect to age, sex, and body weight will be made. Other demographics such as race and ethnicity may be considered for matching the Part 1 and Part 2 populations when possible.

As in Part 1, if there are subjects who withdraw or discontinue treatment from the moderate or mild impairment group and who are considered to be non-evaluable with respect to the primary PK objective, additional subjects can be enrolled at the discretion of the Sponsor.

Screening will occur within a 28-day window prior to dosing. Subjects will be admitted on Day -1; on Day 1 a single SC injection of 5 mg apraglutide will be administered followed by blood PK sampling for 240 hours (Day 11). All subjects who received the apraglutide (including subjects who terminate the trial early) will return to the CRU approximately 14±2 days after dosing for the end of trial (EOT) visit where follow-up assessments will be performed according to the Schedule of Assessments and to determine if any adverse events (AEs) have occurred since the last trial visit.

Figure 1 Trial Schematic



CRU=clinical research unit; PK=pharmacokinetics; SC=subcutaneous

6.1 Sample Size Considerations

No formal power calculation was performed. The number of subjects per group is based on the review of the literature and of the European Medicine Agency (EMA) and the USA Food and Drug Administration (FDA) guidelines. While the EMA suggests 6–8 subjects per group, the FDA draft guidance does not provide an exact number of renal impaired patients needed for such a clinical trial.

The sample size of eight subjects per group is also based on the feasibility to recruit subjects with severe renal impairment.

6.2 Randomization

This is an open-label, single-sequence study; no randomization or blinding will be conducted.

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

There are no changes from the protocol.

7.2 Interim Analysis and Key Results

There will be no interim analyses or summaries of data provided prior to the delivery of the full set of post-lock tables, figures and listings (TFLs).

7.3 Final Analysis

Draft TFLs will be provided after database lock. After Sponsor comments have been incorporated, the TFLs will be finalized and incorporated in the first draft CSR.

8.0 Data Review

8.1 Data Management

Data handling and transfer will take place under the PRA Data Management Plan for the study. All subjects who are screened will be entered in the database.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after database lock. Only quality assured (QA'd) results released by the Safety Laboratory, Bioanalytical Laboratory, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be sent to the project Data Manager. If the issue affects the TFLs the Programmer or Statistician who identified the issue will follow it to resolution.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

9.1.1.1 General

For summaries, the mean and median will be presented to one decimal place greater than the data, standard deviation to 2 greater than the data, and the minimum and maximum will be presented to the same number of decimal places as the data. Percentages will be presented with one decimal.

The above rule can be applied directly to collected data. For derived data rounding will occur prior to summarization (in the derived dataset as determined by the statistician) so a specific number of decimal places will have to be assumed to apply the above rounding rules for summary statistics.

9.1.1.2 Pharmacokinetic

Concentration data will be presented in listings as received by the vendor. Summary statistics of concentration data will be presented to 3 significant digits with the exception of %CV which will be presented to 1 decimal place.

PK parameter data will be rounded in the listings to an appropriate number of decimal places for presentation purposes only. Unrounded values (left as received in analysis dataset) will be used for all calculations of summary statistics and analyses for the summary tables. The summary statistics will be presented to the precision listed in the table in section 16.2.2. When significant digits are used for precision, all summary statistics will be presented to the same precision. When decimal places are used for precision, the rule outlined above in the General rounding section applies for summary statistics.

9.1.2 Imputation

Unless otherwise noted, data will not be imputed.

9.1.3 Daylight Savings Time Adjustments

On March 14, 2021 at 2:00 am the clocks change to 3:00 am for Daylight Savings Time. All clinic procedures for the remainder of the treatment period will be moved forward by one hour after daylight savings time occurs. All duration calculations (ie, AE duration, relative time from dosing for PK) for times post-daylight

savings time that will be relative to a time prior to daylight savings will need to be programmatically adjusted for the hour that was lost on the morning of March 14.

9.1.4 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics and nomenclature: n = number of observations or subjects, mean = arithmetic mean, SD = standard deviation, Min = minimum value, median = median value, and Max = maximum value.

Categorical data will be summarized and presented with the following nomenclature: n = frequency and % = percentage. Percentages by categories will be based on the number of subjects exposed within a treatment.

For categorical data, the categories will be presented in the tables exactly as they appear in the case report form (CRF) / Database.

9.1.5 Pooling

No data pooling will be performed.

9.1.6 Unscheduled Measurements

Unscheduled and early termination measurements will be included in the listings. With the exception of unscheduled measurements used for baseline, unscheduled and early termination measurements will be excluded from the descriptive statistics and statistical analysis.

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline is defined as the last observation recorded before the study drug administration. The last observation can be an unscheduled / repeated measurement.

9.2.2 Treatment/Subject Grouping

Subjects will be assigned to one of the 4 renal function groups based on eGFR values at screening.

Label	Grouping
IMP	Apraglutide (TA799): a single 5 mg dose of apraglutide administered by SC injection to the abdomen.
Renal Function Group	Cohort 1: Severe Renal Impairment Cohort 2: Normal Healthy Match Cohort 3: Moderate Renal Impairment Cohort 4: Mild Renal Impairment

9.2.3 Common Variable Derivations

Variable	Data Type	Definition/Calculation
Change from baseline / predose	All	Postdose Observation minus baseline / predose Observation
Analysis Study Day (Prior to Dose)	All	Date of Measurement minus Dose Date
Analysis Study Day (Post Dose)	All	Date of Measurement minus Dose Date +1

TEAE	AE	AE is a TEAE if the AE Date/Time is greater than or equal to the Dose Date/Time

9.2.4 QC

The analysis datasets and the TFLs will be QC'd according to the general PRA EDS QC plan.

9.2.4.1 Critical Data

The QC plan requires datasets be classified as critical or non-critical. As the primary objective of this study is to characterize the pharmacokinetics, the datasets considered critical are subject level = ADSL, and pharmacokinetic = ADPC and ADPP.

9.2.5 ADaM Datasets and Metadata

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1.

ADaM compliant datasets will be delivered to the sponsor. A define.xml file version 2 with the corresponding metadata will be included. Analysis results metadata are excluded.

9.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ Version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® (WNL) version 8.1 or higher (Certara, L.P.). Additional PK computations may be performed in SAS®.

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

9.4.3 Hypothesis Testing

No formal hypothesis testing will be done.

9.5 TFL Layout

Report layout will be according to the PRA EDS – ICH E3 compliant – CSR Template. The layout of TFLs will be according to the PRA EDS standards.

Table shells are provided with and approved as part of this SAP. Small changes to shell layout due to the nature of the data may be required after lock at the discretion of the PRA project statistician. Other changes to the shells may be out of scope. The TFLs will be provided as a single document in Adobe PDF format (in Letter format), and as individual files for each table, figure and listing in Rich Text Format (.rtf).

10.0 Analysis Sets

The following subject level Analysis Sets (populations) will be used for summaries in the study.

10.1 Safety Set

The Safety Set will consist of subjects who receive at least one dose of the investigational medicinal product (IMP). This set will be used for the safety data summaries and baseline characteristic summaries. This set will be analyzed as treated.

10.2 Pharmacokinetic Concentration Set

The PK concentration set is defined as all subjects assigned to the IMP and treated who have at least one quantifiable concentration measured. This set will be used for PK concentration summaries. This set will be analyzed as treated.

10.3 Pharmacokinetic Parameter Set

The PK parameter analysis set is defined as all subjects assigned to IMP and treated who have at least one of the PK parameters of primary interest measured. This set will be used for PK parameter summaries and primary analysis. This set will be analyzed as treated.

11.0 Subject Disposition

The number and percentage of subjects who completed all screening assessments and enrolled in the study and who didn't complete all screening assessments and didn't enroll in the study and a breakdown of the corresponding reasons for not enrolling in the study, and members of each analysis set will be presented. The number and percentage of subjects who completed and who withdrew from the study prematurely and a breakdown of the corresponding reasons for withdrawal will also be presented. Analysis set, screening data, and study completion data will be listed by subject.

12.0 Protocol Deviations

Protocol deviations will be collected and reported per PRA's Protocol Deviation Management Standard Operating Procedure (SOP) and relevant Work Instruction (WI). Subject-level deviations will be extracted and pulled into the study tabulation model (SDTM) dataset from PRA's Clinical Trial Management. Deviations that have been reported and coded as "Important" will be listed by subject.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

Subject demographics at screening will be summarized by renal function groups. The summary will include the subjects' age (years), sex, race, ethnicity, weight (kg), height (cm), body mass index (BMI) (kg/m^2) and baseline eGFR value. Demographics will be summarized for the Safety Set, PK Concentration Set and PK Parameter Set, if all sets are equivalent then only Safety Set will be presented.

All demographic data as collected during the screening visit will be listed by subject.

13.2 Medical History

Medical history, categorized by preferred term according to MedDRA, will be listed by subject.

13.3 Other Baseline Characteristics

Substance use (illegal drug, tobacco and alcohol) will be listed by subject.

Childbearing potential will be listed by subject.

Non-compliance to in- or exclusion criteria (if any) will be listed by subject.

14.0 Concomitant Medications

Concomitant medications collected on the eCRF as defined by the protocol will be categorized by medication group and subgroup according to WHO Drug Dictionary. All concomitant medications will be listed by subject. Medications with an end date prior to the first dose of study drug will be considered prior medications and will be noted in the listing. If the end date (e.g. partial or missing date) does not confirm that the medication was stopped prior to first dose the medication will not be flagged as prior.

15.0 Treatment Compliance and Exposure

The number and percentage of subjects receiving each dose of study drug will be summarized by renal function group.

Exposure data will be listed by subject.

16.0 Pharmacokinetic Analyses

16.1 Pharmacokinetic Variables

Concentrations of apraglutide will be collected in plasma.

PK parameters of apraglutide will be calculated for plasma.

16.2 Plasma Pharmacokinetic Summaries

16.2.1 Plasma Concentrations

Plasma concentrations of apraglutide below the quantifiable limit (BQL) will be set to 0 in the computation of mean concentration values. Descriptive statistics (number of subjects, mean, geometric mean, SD, coefficient of variation [%CV], median, min, and max) will be used to summarize the plasma concentrations by renal function group at each scheduled timepoint.

Linear (+/-SD) and semi-logarithmic (+SD) plots of the arithmetic mean plasma concentration by scheduled sampling time will be provided by renal function group. These plots will show time in hours. The plots will present all calculated means and will include a reference line for the lower limit of quantification (LLOQ).

Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time will be provided by subject (one subject per page). These plots will show time in hours. Individual plots will use the BQL handling procedure described below for “Plasma Pharmacokinetic Parameters”.

All individual subject plasma concentration data will be listed by subject.

16.2.2 Plasma Pharmacokinetic Parameters

Plasma PK parameters for apraglutide will be estimated using non-compartmental methods with WinNonlin®. The PK parameters will be estimated from the concentration-time profiles, and AUCs will be calculated using linear up / log down method. The points to be included in the λz range will be determined by the pharmacokineticist after inspection of the semi-log concentration-time profiles. At least 3 points will be required to be used. The Cmax data point will not be included.

In estimating the PK parameters, BQL values will be set to zero. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time is missing, the scheduled time will be substituted and flagged.

The following flags will be used to include parameters that meet the predefined criteria for summary and analysis.

Criteria Name	Criteria
Extrapolation	AUC%Extrap <= 20%
Regression	Adj Rsq >= 0.8
Lz1	Lz_Start (parent only) >= 2*Tmax
Span	Span > 2

Note: Flags will be applied to parameters prior to derivation of additional parameters in SAS and will be used to include derived parameters as well.

Parameter	Description	SAS Programming Notes	Summary Statistic Reporting Precision*
Cmax	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	Cmax from WNL	3 significant digits
Tmax	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	Tmax from WNL	2 decimal places
AUClast	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	AUClast from WNL	3 significant digits
AUCinf	Area under the concentration-time curve from time 0 extrapolated to infinity.	AUCINF_obs from WNL To be included in analysis/summaries if the following criteria are met: • Extrapolation, • Regression	3 significant digits
AUC0-7days	Area under the concentration-time curve from time 0 to Day 7 postdose inclusive. Equivalent to AUC0-168h	AUC0-168h from WNL From summary file To be included in analysis/summaries if the actual time for the Day 7 timepoint has a time deviation < 10%.	3 significant digits

T-HALF	Terminal elimination phase half-life expressed in time units. T- HALF, will be calculated as ln(2)/Lz, where Lz is as defined below.	HL_Lambda_z from WNL To be included in analysis/summaries if the following criteria are met: • Extrapolation • Regression • Lz1 • Span	3 decimal places
CL/F	Apparent clearance after extra-vascular (EV) dose.	CL_F_obs from WNL To be included in analysis/summaries if the following criteria are met: • Extrapolation, • Regression	3 significant digits
Vz/F	Apparent volume of distribution after extra-vascular dose.	Vz_F_obs from WNL To be included in analysis/summaries if the following criteria are met: • Extrapolation, • Regression	3 significant digits

*Parameters with 'decimal place' precision will follow the General rule for summary statistics rounding with the number of decimal places noted as the starting point.

Descriptive statistics (number of subjects, mean, geometric mean, SD, %CV, median, min, and max) will be used to summarize the calculated PK parameters by renal function group. For Tmax, only median, min and max will be presented.

A scatter plot of individual (plus mean and median) PK parameters Cmax, AUClast and AUCinf by renal function group will be provided.

Box and whisker plots for individual subject parameters (AUCinf or AUClast and Cmax) will be constructed by renal function group and overlaid with geometric means.

All parameters will be listed by subject, parameters that meet the inclusion criteria will be accompanied by an indication that each is criteria met.

The following parameters are used for diagnostics and thus listed but not summarized.

Parameter	Description	SAS Programming Notes
AUC%Extrap	Percentage of AUCinf due to extrapolation from the last quantifiable concentration observed to infinity. AUC%Extrap = [AUCinf – AUClast]/AUCinf * 100	AUC_%Extrap_obs from WNL
Adj Rsq	Goodness of fit statistic for the log-linear terminal elimination phase of the concentration-	Rsq_adjusted from WNL

	time profile identified by least-squares linear regression and adjusted for the number of points (minimum of 3) used in the estimation of Lz.	
Lz	First-order rate constant associated with the terminal (log-linear) portion of the curve. Estimated by linear regression of time vs. log concentration	Lambda_z from WNL
Lz_Start	Lz_Start is the start time used in the regression for the determination of Lz.	Lambda_z_lower from WNL
Lz_End	Lz_End is the end time used in the regression for the determination of Lz.	Lambda_z_upper from WNL
Lz_N	Lz_N is the number of points used in the regression for the determination of Lz.	No_points_lambda_z from WNL
Span	The minimum number of half-lives needed for the Lz range to be acceptable.	Span from WNL

16.2.2.1 Statistical Analyses

Part 1:

Analysis of variance (ANOVA) will be used to compare the natural log transformed AUCinf or AUClast (if AUCinf cannot be calculated) and Cmax for apraglutide between normal renal function group (Reference) and the severe impaired renal group (Test). Estimates of the mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the GMR (Test/Reference) and 90% CIs for the ratios.

The following SAS PROC MIXED pseudo-code may be used:

```
proc mixed data = adpp;
   by analyte parameter;
   class renal_group;
   model ln(aval) = renal_group;
   lsmeans renal_group / cl alpha = 0.1;
   estimate "Severe renal impairment vs Normal renal function" renal_group -1
1 /e cl alpha=0.1;
run;
```

Part 2 (if conducted):

Analysis of variance will be used to compare the natural log transformed AUCinf or AUClast and Cmax for apraglutide between normal renal function group from Part 1 (Reference) and each of the moderate and mild impaired renal groups (Test). Estimates of the mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the GMR (Test/Reference) and 90% CIs for the ratios.

The following SAS PROC MIXED pseudo-code may be used:

```
proc mixed data = adpp;
   by analyte parameter;
   class renal_group;
   model ln(aval) = renal_group;
   lsmeans renal_group / cl alpha = 0.1;
```

```
   estimate "Moderate renal impairment vs Normal renal function" renal_group
0 -1 0 1 /e cl alpha=0.1;
   estimate "Mild renal impairment vs Normal renal function" renal_group 0 -1
1 0 /e cl alpha=0.1;
run;
```

If Part 2 is executed and data for normal, mild, moderate and severe impairment groups are available, additional analysis will be performed to assess relationship between appropriate PK parameters and renal function. The estimates of the GMR (Test/Reference) and 90% CIs for the ratios for AUC will be plotted for all three renal impairment groups (mild, moderate and severe). Linear regression analyses will be used to model the relationship between log-transformed PK parameters derived from subjects with normal renal function and those with mild, moderate or severe renal impairment (namely AUCinf or AUClast and Cmax) and eGFR measured at screening, potentially accounting for age, sex, race and weight. The regression model will have log-transformed PK parameters as response variable, and include independent variable eGFR, and covariates age, sex, race and weight in the model.

The following SAS PROC MIXED pseudo-code may be used:

```
proc mixed data = adpp;
   by analyte parameter;
   class sex race;
   model ln(aval) = eGFR age sex race weight/ cl alpha=0.1;
run;
```

17.0 Safety Analyses

17.1 Safety Variables

- Adverse Events (AEs)
  - AESIs
  - Serious AEs (SAEs)
- Clinical Laboratory Evaluations
  - Clinical Chemistry
  - Hematology
  - Urinalysis
  - Serum Creatinine and eGFR
- Vital Signs
  - Supine Blood Pressure
    - Systolic Blood Pressure
    - Diastolic Blood Pressure
  - Pulse Rate
  - Body temperature
- Electrocardiograms (ECG)
  - Heart Rate
  - PR Interval
  - QRS-Duration
  - QT Interval
  - RR Interval
  - QTc (Bazett) Interval
  - QTc (Friderica) Interval

17.1.1 Adverse Events

Treatment emergence will be evaluated for all AEs. Treatment-emergent adverse events (TEAE) are those that occur after the dose of study drug.

The following missing data will be imputed as defined (for calculations/summary tables only and will not be presented in listings):

- Missing AE start and / or end times for the calculation of onset and duration will be assumed to be at 00:01 for a start time and 23:59 for end times
- Missing AE severity or relationship will be assumed to be severe or related, respectively
- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing AE start date will be assumed to be after treatment for the determination of TEAE

A summary of number and percentage of subjects reporting TEAEs, TEAEs by severity and relationship, serious AEs (SAEs), and subjects who discontinued study drug due to an AE will be provided.

A summary of the number and percentage of subjects reporting each TEAE, and summary of total number of events, categorized by system organ class and preferred term coded according to the MedDRA, will be presented by renal function group and overall. Subjects will only be counted once within each body system or preferred term.

A summary of the number and percentage of subjects reporting each TEAE, and summary of total number of events, will be presented by relationship to study drug (as recorded on the eCRF) and by renal function group and overall. Subjects with multiple events within a system organ class or preferred term will be counted under the category of their most drug-related event within that system organ class or preferred term.

A summary of the number and percentage of subjects reporting each TEAE, and summary of total number of events, will be presented by severity (as recorded on eCRF) and by renal function group and overall.

Subjects with multiple events within a system organ class or preferred term will be counted under the category of their most severe event within that system organ class or preferred term.

A summary of the number and percentage of subjects reporting each SAE, and summary of total number of events , categorized by system organ class and preferred term coded according to the MedDRA, will be presented by renal function group and overall. Subjects will only be counted once within each body system or preferred term.

A summary of the number and percentage of subjects reporting each AESI, and summary of total number of events , categorized by system organ class and preferred term coded according to the MedDRA, will be presented by renal function group and overall. Subjects will only be counted once within each body system or preferred term.

All AEs (including non-treatment-emergent events) recorded on the eCRF will be listed by subject.

A separate listing of AEs leading to study drug discontinuation will be provided.

17.1.2 Deaths and Serious Adverse Events

A listing of deaths and other SAEs will be provided by subject.

17.1.3 Laboratory Data

Clinical laboratory data will be presented using units from SDTM Controlled Terminology.

Descriptive statistics summarizing continuous laboratory results of clinical chemistry, hematology, and urinalysis and changes from baseline by renal function group and scheduled time will be provided. Serum creatinine and eGFR will be summarized separately.

Drug-induced liver injury (DILI) will be listed by subject.

All laboratory data will be listed by subject, including laboratory tests not listed in the protocol. A separate listing of out-of-range values will also be provided. Normal ranges will be used directly from the clinical laboratory and will be included in the listings for reference.

17.1.4 Vital Signs

Descriptive statistics summarizing vital signs and changes from predose by renal function group and scheduled time will be provided.

All vital signs will be listed by subject.

17.1.5 Electrocardiograms

The observed measurements for all ECG parameters and the corresponding abnormalities will be listed by subject. The means of triplicate measurements for continuous parameters and the change from predose of the mean triplicate measurements at each scheduled timepoint will also be listed by subject.

Descriptive statistics summarizing mean ECG parameters and changes from predose by renal function group and scheduled time will be provided. The overall interpretation of the ECG results at each scheduled time will be summarized by the number and percentage of subjects in each category (Normal, Abnormal - Not Clinically Significant (NCS) and Abnormal – Clinically Significant (CS)). The predose and postdose ECG interpretation will be the most abnormal and clinically significant interpretation among the triplicates if the interpretations are not the same.

17.1.6 Other Observations Related to Safety

All physical examination data will be listed by subject.

Injection site evaluation data will be listed by subject.

Contraception check results will be listed by subject.

18.0 References

SAS Institute, Inc., SAS® Version 9.4 software, Cary, NC.

Clinical Study Protocol. 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. Version 3.0, Final, 11 Sep 2020.

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
AESIs	AE of Special Interest
ADaM	Analysis data model
ANOVA	Analysis of variance
BMI	Body mass index
BP	Blood pressure
BQL	Below the quantifiable limit
CDISC	Clinical Data Interchange Standard Consortium
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology
CSR	Clinical study report
CS	Clinically significant
CRF	Case Report Form
CV	Coefficient of variation
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Early Development Services
eGFR	Estimated glomerular filtration rate
EMA	European Medicine Agency
EOT	End of trial
FDA	Food and Drug Administration
GMR	Geometric mean ratio
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational medicinal product
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
PK	Pharmacokinetic
QA'd	Quality assured
QC'd	Quality controlled
SAP	Statistical analysis plan

SAE	Serious adverse event
SC	Subcutaneous
SCr	Serum creatinine
SD	Standard deviation
SDTM	Study data tabulation model
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TFL(s)	Tables, figures and listings
WI	Work Instruction
WNL	WinNonlin

Appendix 2: Protocol Schedule of Assessments

Visit Identifier[a]	Screening Visit 1[b] Day-28 to Day -1	Screening visit 2[b]	D -1[b]	D 1	D 2	D3	D 4	D 5	D 6	D 7	D 8	D 11	D 14±2 days End of Trial/Early Termination
Informed Consent	x												
Instruct Subjects on lifestyle requirements and restrictions	x										x		
Admission to CRU			x										
Confinement to CRU			x	x	x	x	x	x	x	x	x		
Medical History	x		x[o]										
Inclusion/Exclusion	x		x										
Demography[c]	x												
Physical examination[d]	x		x			x					x		x
Height and weight assessment for BMI[e]	x	x	x										x
Safety Laboratory tests (blood, urine)[f] (Optional HbA1C, TSH)	x		x		x						x	x	x
eGFR assessment[g]	x	X	x								x	x	
Serum pregnancy test (women of child bearing potential only)	x		x										x
Contraception check[h]	x	x	x								x		x
Serum FSH in postmenopausal females with amenorrhea ≥12 months and under 60 years of age and not using hormonal contraception or hormone replacement therapy	x												
Urine drug and/or alcohol test[i]	x		x										
Triplicate ECG[j]	x		x	x	x						x	x	x
Vital Signs (supine BP, heartrate) and body temperature[k]	x		x	x[p]	x	x	x	x	x	x	x	x	x
HIV, HBsAg, HCV core Ab testing	x												
Apraglutide administration				x									
Injection site assessment[l]				x	x	x	x	x	x	x	x		x
Plasma PK for apraglutide[m]				x	x	x	x	x	x	x	x	x	
Prior and Concomitant treatment	x	x	x	x	x	x	x	x	x	x	x	x	x
CRU discharge											x		

AEs/AESIs/SAEs monitoring	x	x	x	x	x	x	x	x	x	x	x	x	x
Fasting[n]			x										

AE=adverse event; AESI=adverse event of special interest; Ag=antigen; BMI=body mass index; CRU=clinical research unit; D=day; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; FSH=follicular stimulating hormone; HbA1c=glycated hemoglobin; HB=hepatitis B; HCV=hepatitis C virus; HIV=human immunodeficiency virus; SAE=serious adverse event; TSH=thyroid stimulating hormone.

a. Day relative to start of trial treatment (Day 1).
b. Screening will consist of up to two CRU outpatient visits (Screening 1 and Screening 2) between 3 and 14 days apart, with the first Screening visit occurring within 28 days prior to investigational medicinal product administration (Day 1). The second screening visit is only to demonstrate stable renal function with difference between eGFRs at Screening visit 1 (S1) and Screening visit 2 (S2) is required to be ≤25% of the value obtained at S1. A historical eGFR using CKD-EPI can be used to demonstrate stability if value is within 3 months prior to S1. If no historical value within that timeframe is available, the subject will be assessed at S1 and S2 per protocol. Note that the second eGFR calculation may occur at admission visit (Day -1) as long as this visit falls within the 3- to 14-day range following S1 collection. Other screening procedures completed during the first visit (S1) do not need to be repeated. Maximum delay accepted between screening and IMP administration is a total of 42 days.
c. Demographics include race, age and sex, ethnicity and date of birth.
d. Complete physical examination (PE) at S1 and abbreviated PE at Day -1. If a complete PE was not completed at S1 visit, then complete PE must be done at Day -1. Symptom-driven PE only at Day 3. Abbreviated PE on discharge (Day 8) and Follow-up (Day 14 or Early Termination visit.)
e. Height to be obtained only at S1. BMI will be calculated at S1 only. Weight to be obtained at S1, S2, Day -1 and Day 14.
f. Safety laboratory assessments include chemistry, hematology, and urinalysis (and microscopy, if needed) and will be performed at S1, on Day -1, Day 2, Day 8, Day 11, and Day 14 or Early Termination visit. All assessments must be performed after at least an 8-hour fast. At Day -1, the results must have no clinically significant findings as per the Investigator's judgment to allow investigational medicinal product administration on Day 1. An optional HbA1c and TSH will be allowed at Screening, if applicable, per the discretion of the Investigator to confirm stability of concurrent medical conditions (for Cohorts 1 [severe], 3 [moderate] and 4 [mild] only).
g. To confirm eligibility, participants must have stable renal function defined as ≤25% difference for eGFR values at S2 compared to the value at S1. The average of the two screening eGFR values will be used for participant stratification and group assignment (provided stable renal function is still demonstrated). A historical eGFR using CKD-EPI can be used to demonstrate stability if the value is within past 3 months. If none available, the subject will be assessed at S1 and S2 per protocol. If the renal function stability criterion is met but the renal function classification category changes between S1 eGFR and the average of the S1 and S2 eGFRs, the eGFR measurement at Day -1 will also be used to determine the appropriate group classification category using an average of all three eGFR values, to determine whether the participant will be eligible for enrollment. The Day -1 eGFR value will be used for pharmacokinetic analysis. The eGFR determination will utilize the CKD-EPI equation.
h. Confirmation of appropriate use only.
i. This test may be performed at any other time at the discretion of the Investigator.
j. Triplicate 12-lead ECG will be performed after supine rest of 10 minutes at Screening, Day -1, Day 1 pre-dose, Day 1 (4 hours), and Day 2 (24 hours) and again on Day 8, Day 11, and Day 14. Electrocardiogram should be obtained within 45 minutes of dosing on Day 1.
k. Obtain blood pressure and heart rate measurements after at least 5 minutes of rest in a supine position. One repeat measurement may be allowed at the discretion of the Investigator.
l. Injection site reaction assessments will be performed pre-dose and 4, 24, 48, 72, 96, 120, 144, and 168 hours post dose, as well as at Early Termination or Day 14.
m. Pharmacokinetic time points will be as follows: 0 (5 minutes pre-dose), 6, 12, 24, 28, 36, 40, 48, 60, 72, 96, 120, 144, 168, and 240 hours.
n. Subjects will be instructed to begin fasting 8 hours prior to Day 1 dose of apraglutide.
o. Changes since Screening.
p. Vitals signs on Day 1 at pre-dose, 1 hour and 4-hour time points. Vital Signs should be obtained within 45 minutes prior to dosing on Day 1.

Appendix 3: List of End of Text Outputs

List of End of Text Tables and Figures:		
Output	**Title**	**Analysis Set**
Section 14.1 – Disposition and Demographic Data		
Table 14.1.1	Summary of Subject Disposition	All Subjects
Table 14.1.2.1	Summary of Demographics	Safety
Table 14.1.2.2	Summary of Demographics	PK Concentration
Table 14.1.2.3	Summary of Demographics	PK Parameter
Table 14.1.3	Summary of Study Drug Administration	Safety
Section 14.2 – Pharmacokinetic Data		
Table 14.2.1	Summary of Apraglutide Plasma Concentrations	PK Concentration
Table 14.2.2	Summary of Apraglutide Plasma Pharmacokinetic Parameters	PK Parameter
Table 14.2.3.1	Analysis of Variance of Pharmacokinetic Parameters	PK Parameter
Figure 14.2.3.2	Plot of GMR and 90% CIs for the Test/Reference ratios	PK Parameter
Table 14.2.3.3	Statistical Analysis (Linear Regression) of Primary PK Parameters and eGFR	PK Parameter
Figure 14.2.4.1	Plot of Mean (± SD) Apraglutide Plasma Concentrations Versus Time on a Linear Scale	PK Concentration
Figure 14.2.4.2	Plot of Mean (+SD) Apraglutide Plasma Concentrations Versus Time on a Semi-Log Scale	PK Concentration
Figure 14.2.5.1	Plot of Individual Apraglutide Plasma Concentrations Versus Time on a Linear Scale	PK Concentration
Figure 14.2.5.2	Plot of Individual Apraglutide Plasma Concentrations Versus Time on a Semi-Log Scale	PK Concentration
Figure 14.2.6.1	Scatter Plot of Individual Plasma Pharmacokinetic Parameters	PK Parameter
Figure 14.2.6.2	Box Plot of Individual Plasma Pharmacokinetic Parameters	PK Parameter
Section 14.3 – Safety Data		
Table 14.3.1.1	Summary of Adverse Events	Safety
Table 14.3.1.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety
Table 14.3.1.3	Summary of Treatment Emergent Adverse Events by Relationship to Study Drug	Safety
Table 14.3.1.4	Summary of Treatment Emergent Adverse Events by Severity	Safety
Table 14.3.1.5	Summary of Serious Adverse Events by System Organ Class and Preferred Term	Safety

Table 14.3.1.6	Summary of Adverse Events of Special Interest by System Organ Class and Preferred Term	Safety
Table 14.3.2	Listing of Deaths and Other Serious Adverse Events	All Subjects
Table 14.3.4	Listing of Abnormal Laboratory Values	All Subjects
Table 14.3.5.1	Summary of Laboratory Results	Safety
Table 14.3.5.2	Summary of Serum Creatinine and Estimated Glomerular Filtration Rate	Safety
Table 14.3.6	Summary of Vital Signs	Safety
Table 14.3.7	Summary of Mean 12-Lead Electrocardiogram Results	Safety

List of End of Text Listings:	
Output	**Title**
Section 16.2.1 – Disposition	
Listing 16.2.1.1.1	Subject Disposition
Listing 16.2.1.1.2	Screening
Listing 16.2.1.2	Eligibility Criteria
Section 16.2.2 – Protocol Deviations	
Listing 16.2.2	Important Protocol Deviations
Section 16.2.3 – Excluded Subjects	
Listing 16.2.3	Analysis Sets
Section 16.2.4 – Demographics and Baseline Characteristics	
Listing 16.2.4.1	Subject Demographics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3	Prior and Concomitant Medications
Listing 16.2.4.4	Substance Use
Listing 16.2.4.5	Childbearing Potential
Section 16.2.5 – Compliance	
Listing 16.2.5	Study Drug Administration
Section 16.2.6 – Response Data	
Listing 16.2.6.1	Apraglutide Plasma Concentrations
Listing 16.2.6.2	Apraglutide Plasma Pharmacokinetic Parameters
Listing 16.2.6.3	Apraglutide Plasma Pharmacokinetic Diagnostic Parameters
Section 16.2.7 – Adverse Events Data	
Listing 16.2.7.1	Adverse Events
Listing 16.2.7.2	Adverse Events Leading to Study Drug Discontinuation

Section 16.2.8 – Laboratory Data	
Listing 16.2.8.1	Clinical Laboratory Results – Chemistry
Listing 16.2.8.2	Clinical Laboratory Results – Hematology
Listing 16.2.8.3	Clinical Laboratory Results – Urinalysis
Listing 16.2.8.4	Clinical Laboratory Results – Additional Assessments
Listing 16.2.8.5	Clinical Laboratory Results – Serum Creatinine and Estimated Glomerular Filtration Rate
Listing 16.2.8.6.1	Drug-induced Liver Injury – Environmental Risks and International Travel
Listing 16.2.8.6.2	Drug-induced Liver Injury – Signs or Symptoms
Listing 16.2.8.6.3	Drug-induced Liver Injury – GI Findings and Alternate Etiology
Section 16.2.9 Onward – Other Safety Data	
Listing 16.2.9	Vital Signs
Listing 16.2.10.1	12-Lead Electrocardiogram Results
Listing 16.2.10.2	Mean 12-Lead Electrocardiogram Results
Listing 16.2.11	Physical Examination Findings
Listing 16.2.12	Injection Site Evaluation
Listing 16.2.13	Contraception Check

Other Appendix Outputs:	
Output	**Title**
Appendix 16.1.9.2.1	Statistical Methods and Analysis Output 1
Appendix 16.1.9.2.2	Statistical Methods and Analysis Output 2

Appendix 4: Shells for Post-Text Tables, Figures and Listings

Shells are provided in a separate document.

19.0 Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
02-Nov-2020	[redacted]	Initial created from [redacted].