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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Clinical Trial 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

Trial Type:	Phase 1
IND:	To be inserted
Trial Identifier:	TA799-014
Sponsor:	VectivBio AG Aeschenvorstadt 36 4051 Basel Switzerland
Investigational medicinal product	Apraglutide (TA799)
Protocol Version and Date	Version 4.0, 11-JAN-2021
Contract Research Organization	Pharmaceutical Research Associates Inc. 4130 Parklake Avenue, Suite 400 Raleigh, NC 27612 USA

The trial will be conducted according to this protocol and in compliance with Good Clinical Practice (GCP) [1], with the Declaration of Helsinki [2], the FDA regulations [3] and with other applicable regulatory requirements.

Declaration of Sponsor's Responsible Medical Officer

This trial protocol was subject to critical review. The information it contains is consistent with current knowledge pursuant to the risks and benefits of the investigational medicinal product, as well as with the moral, ethical principles governing clinical research as set out in the Declaration of Helsinki [2]. FDA regulations [3] and all guidelines on GCP [1].

I approve this protocol on behalf of the Sponsor.

[redacted]
SVP Head of Clinical Development and Medical Affairs
[redacted]

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List of Abbreviations and Definition of Terms

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate transaminase
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CIC	Colon In Continuity
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology
CQ	Customer Queries
CRU	Clinical research unit
CTR	Clinical Trial Report
CV	Coefficient of variation
CYP	Cytochrome P450
DILI	Drug-induced liver injury
DPP4	Dipeptidyl peptidase-4
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicine Agency
EOT	End of trial
ET	Early termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GMR	Geometric mean ratio
GLP	Glucagon-like peptide
HbA1c	Glycated hemoglobin
HBsAg	Surface antigen of the hepatitis B virus (HBV)
HBcAb	Hepatitis B core antibody
HCVAb	Hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
ICF	Informed consent form

ICH	International Council for Harmonisation (formerly known as International Conference on Harmonisation)
ID	Identifier
IF	Intestinal failure
IMP	Investigational medicinal product
IRB	Institutional Review Board
ISR	Injection site reaction
IV	Intravenous(ly)
KDOQ	Kidney disease outcomes quality initiative
LFT	Liver function test
MedDRA	Medical dictionary for regulatory activities
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
PD	Pharmacodynamic(s)
PE	Physical examination
PK	Pharmacokinetic(s)
PS	Parenteral support
QT	Interval between Q-wave and T-wave
QTcF	Fridericia's correction
ΔQTcF	Changes from baseline in QTcF
ΔΔQTcF	Placebo-corrected changes from baseline in QTcF
QW	Once per week
SAE	Serious adverse event
SAP	Statistical analysis plan
SBS	Short bowel syndrome
SBS-IF	SBS with intestinal failure
SBS-II	SBS with intestinal insufficiency
SC	Subcutaneous
SMQ	Standardized MedDRA query
SUSAR	Suspected unexpected serious adverse event
$t_{1/2}$	Terminal half-life
TBili	Total bilirubin
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WFI	Water For Injection
WOCBP	Women of child-bearing potential
WHO	World Health Organization

Protocol synopsis

Title of trial
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

Trial sites
Two trial sites will participate:
Prism Clinical Research, Inc. in St Paul, MN, USA
Orlando Clinical Research Center in Orlando, FL, USA

Planned trial period	**Clinical phase**
Part 1 of Clinical Trial Estimated First subject first visit: November 2020 Estimated Last subject last visit: March 2021 **Part 2 of Clinical Trial (if applicable)** Estimated start: May 2021 Estimated completion: September 2021	Phase 1

Objectives

Primary objective

- Part 1 of clinical trial: To assess the pharmacokinetics (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; see criteria to move to Part 2 in Section 3.1.1): 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

Trial design

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 [16]:

$eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]
Notes eGFR is expressed as mL/min/1.73 m^2 of body surface area, SCr (serum creatinine) is expressed as mg/dL, $\kappa = 0.7$ (females) or 0.9 (males), $\alpha = -0.329$ (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.

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. 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: Part 2 will be conducted if after evaluation from Part 1, the point estimate of apraglutide area under the concentration-time curve from time 0 to infinity (AUC_{inf}) or to the time of the last quantifiable concentration AUC_{last} geometric mean ratio (GMR) for the severe renal impairment group compared to the control group is ≥2 (Section 3.1.1).

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 [15]. Healthy subjects from Part 1 will be used as the control group of the moderate and mild renal impairment subjects. When recruiting Part 2 subjects, attempts to match the entire group to the subjects in Part 1 with respect to age and body weight will be made. Other demographics such as race and ethnicity will be taken into consideration when possible.

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.

Number of Subjects

Part 1

Cohort	eGFR (ml/min/1.73m^2)*	N
1 (Severe Renal Impairment)	<30 not on hemodialysis**	8
2 (Normal Healthy Match)	≥90	8

Part 2

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

*Estimated glomerular filtration rate based on CKD-EPI. The baseline eGFR will be calculated 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.
**Reasonable efforts will be made to enroll at least two subjects with eGFR values of <20 mL/min/1.73 m^2

Inclusion/Exclusion Criteria

Inclusion Criteria

- **All Subjects**

Subjects are eligible to be included in the trial only if all of the following criteria apply:

Age and Sex

1. Male or female subjects who are between the ages of 18–75 years, inclusive, at Screening

Type of Subject and Disease Characteristics

2. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other trial procedures
3. Body mass index (BMI) of ≥17.5 to ≤40 kg/m^2; and a total body weight of >50 kg (110 lb)
4. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol
5. Women of childbearing potential must agree to practice effective contraception and to use a highly effective method of contraception during the trial and for 1 month after the EOT visit. Such methods include: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner. To be considered sterilized or infertile, females must have undergone surgical sterilization (bilateral tubectomy, hysterectomy, or bilateral ovariectomy) or be postmenopausal (defined as at least 12 months amenorrhea; it may be confirmed with follicle-stimulating hormone test if there is doubt and/or the woman is under 60 years of age and not using hormonal contraception or hormone replacement therapy)
6. Male subjects with a female partner of childbearing potential must commit to practice highly effective methods of contraception (e.g., condom) and abstain from sperm donation during the trial and for 1 month after the EOT visit

- **Additional Inclusion criteria for Healthy Subjects with Normal Renal Function (Cohort 2 only)**

7. No clinically relevant abnormalities identified by detailed medical history, full physical examination, including body temperature, blood pressure (BP), and heart rate measurement, 12-lead electrocardiogram (ECG), and clinical laboratory tests
8. Normal renal function (average eGFR measured by CKD-EPI ≥90 mL/min/1.73 m^2) at two screening visits where Screening 2 can be performed at admission on Day -1
9. Demographically comparable to the group of subjects with impaired renal function:
   a. That each subject's age within ±10 years of the mean age and ±15 kg of the severe renal impairment cohort (Cohort 1)
   b. Attempts will be made to ensure that the male-to-female composition of Cohort 2 is comparable to that in the severe renal impairment cohort (Cohort 1)
   c. Other demographic characteristics such as race and ethnicity matched as closely as possible to the renal impairment cohort

- **Additional Inclusion criteria for Subjects with Impaired Renal function (Cohort 1 and Cohorts 3 and 4 [if applicable] only)**

10. Good general health commensurate with the population with chronic kidney disease (renal impairment). "Health" is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, measurement of heart rate and 12-lead ECG, as well

as clinical laboratory tests (except serum creatinine and eGFR). Hypertension, diabetes mellitus, hyperparathyroidism, ischemic heart disease and other common co-morbidities in this population are possible exemptions, as long as, in the opinion of the Investigator, the subject is medically stable, is on a stable drug regimen, and can abide by the meals and dietary restrictions outlined in protocol in Section 4.3

11. Meet the following eGFR criteria (based on average) during the screening period based on the CKD-EPI equation:
    a. Severe renal impairment: eGFR <30 mL/min/1.73 m^2, but not requiring hemodialysis
    b. Moderate renal impairment (Part 2 only): eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2
    c. Mild renal impairment (Part 2 only): eGFR ≥60 and <90 mL/min/1.73 m^2

    The eGFR values obtained during screening visits should not be more than 25% different for Cohort 1 (severe), Cohort 3 (moderate), and Cohort 4 (mild)
12. Any form of renal impairment except acute nephritic syndrome or nephrotic syndrome defined as proteinuria >3 g (subjects with history of previous nephritic syndrome but in remission can be included)
13. Stable concomitant drug regimen (as defined in Section 6.2) for the management of individual subject's medical conditions

Exclusion Criteria

- **All Subjects**

Subjects excluded from the trial if any of the following criteria apply:

Medical Conditions

1. Renal transplant recipients
2. History of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the Investigator within 3 months prior to Screening and Day 1
3. Any active malignancies or history of malignancies within the past 2 years prior to screening with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma *in situ*
4. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation, or behavior that may increase the risk associated with trial participation or investigational medicinal product (IMP) administration or may interfere with the interpretation of trial results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this trial
5. Treatment with an IMP within 30 days or five half-lives, if known, (whichever is longer) preceding the dose of IMP
6. Male subjects who are unable to comply with the following requirements during the intervention period and up to 1 month after the dose of apraglutide, which corresponds to the time needed to eliminate trial interventions:
    a. Refrain from donating sperm
    b. PLUS, either be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle abstinent on a long-term persistent basis and agree to remain abstinent
    c. OR must agree to use a male condom with spermicide when engaging in any activity that allows for passage of ejaculate to another person
    d. Vasectomy

7. A history of clinically significant intestinal adhesions and/or chronic abdominal pain
8. History of known colon polyps or family history of familial adenomatous polyposis

Diagnostic Assessments

9. Positive blood screen for hepatitis C antibody, hepatitis B surface antigen or human immunodeficiency virus (HIV)-1 and -2 antibodies
10. ANY of the following abnormalities in clinical laboratory tests at Screening, and confirmed by a single repeat, if deemed necessary:
    a. Serum albumin concentration <25 g/L (2.5 g/dL)
    b. Hemoglobin concentration <90 g/L (9.0 g/dL)
    c. Enzymes aspartate amino transaminase (AST) or alanine amino transaminase (ALT) values >2 × upper limit of normal (ULN)
    d. Proteinuria of >3 g total bilirubin >1.5 × ULN; subjects with Gilbert's syndrome would be eligible for this trial provided the direct bilirubin is ≤ULN
11. In the opinion of the Investigator (or designee), subjects have any clinically significant laboratory abnormality that could affect interpretation of trial data or the subject's participation in the trial. Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results (with the same screening number); the last value will be used to determine eligibility
12. Positive urine test for alcohol or illicit drugs at either Screening or admission. Renal impairment subjects may be eligible to participate after approval from Sponsor if their drug screen is positive for a prescribed substance that is not expected to interfere with the PK of apraglutide
13. Screening 12-lead ECG in triplicate that demonstrates:
    a. Clinically significant abnormalities requiring treatment (e.g., acute myocardial infarction, serious tachy- or brady-arrhythmias) or indicating serious underlying heart disease (e.g., cardiomyopathy, Wolff-Parkinson–White syndrome)
    b. Confirmed QT interval corrected using Frederica's correction factor (QTcF) >450 msec for subjects with normal renal function and >480 msec for subjects with impaired renal function
    c. Long QT Syndrome, a family history of Long QT Syndrome, or a history of Torsades de Pointes

Prior/Concomitant Therapy

14. Use of prescription or non-prescription drugs and dietary supplements within 7 days or five half-lives (whichever is longer) prior to Day 1
    Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the trial may be permitted on a case by case basis following approval by the Investigator in consultation with the Sponsor
    Herbal supplements must be discontinued at least 28 days prior to the dose of IMP
    For subjects with renal impairment, stable concomitant medications (including herbal supplements) may be given if they are considered necessary for the welfare of the subjects (e.g., standard therapy for underlying diseases), and are not contraindicated with the IMP or likely to interfere with the PK of the IMP. Stable is defined as no changes in current medications or starting new medications for 14 days prior to apraglutide administration

Other Exclusion Criteria

15. Investigator site staff members directly involved in the conduct of the trial and their family members, or any site staff members otherwise supervised by the Investigator
16. History of regular alcohol consumption exceeding seven drinks/week for females or 14 drinks/week for males (1 drink = 5 ounces [150 mL] of wine, or 12 ounces [360 mL] of beer, or 1.5 ounces [45 mL] of hard liquor) within 3 months of Screening
17. Female subjects of childbearing potential who are unwilling or unable to use highly effective

methods of contraception, as outlined in the protocol, for the duration of the trial and for at least 1 month after the administration of the IMP; pregnant female subjects; female subjects planning to become pregnant during the duration of the trial and until 1 month after the administration of the IMP; breastfeeding female subjects

18. Blood donation of approximately 1 pint (500 mL) or more within 60 days prior to the dose of IMP. Plasma donations of approximately 1 pint (500 mL) or more within 28 days prior to the dose of IMP
19. History of sensitivity to heparin or heparin-induced thrombocytopenia, *only if* heparin is used to flush intravenous (IV) catheters used during serial blood collections
20. Unwilling or unable to comply with the Lifestyle Considerations outlined in Section 4.3

- **Additional Exclusion Criteria for Healthy Subjects with Normal Renal Function (Cohort 2 only)**

21. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing)
22. Evidence or history of clinically significant dermatological condition (in the opinion of the Investigator) or visible rash present during physical examination

- **Additional Exclusion Criteria for Subjects with Impaired Renal Function (Cohort 1 and Cohorts 3 and 4 [if applicable] only)**

23. Subjects requiring hemodialysis and/or peritoneal dialysis
24. Subjects with other clinically significant disease that may affect the safety of the subject or that may affect the PK of apraglutide (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing)
25. Subjects with any significant hepatic, cardiac, or pulmonary disease or subjects who are clinically nephrotic. Hypertension, diabetes mellitus, hyperparathyroidism, ischemic heart disease, etc. are not cause for exclusion as long as, in the opinion of the Investigator, the subject is medically stable and any drugs that are administered for these conditions are not expected to interfere with the PK of apraglutide
26. Screening BP ≥180 mmHg (systolic) or ≥110 mmHg (diastolic), following at least 5 minutes of supine rest. If initial BP is ≥180 mmHg (systolic) or ≥110 mmHg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the subject's eligibility. An additional set of vital signs can be obtained at the discretion of the Investigator

Investigational medicinal product

Apraglutide (TA799): Freeze-dried powder (12.5 mg) for reconstitution in sterile water prior to SC injection

Duration of treatment

Each subject will receive a single 5 mg dose of apraglutide administered by SC injection to the abdomen.

Endpoints

Primary endpoints

Plasma apraglutide PK parameters: C_{max} and $AUC_{inf.}$, AUC_{last} $AUC_{0\text{-}7days}$, T_{max}, λ_z, $t_{½}$, CL/F, V_z/F. C_{max} and AUC_{inf} or AUC_{last} as primary PK parameters. All others as secondary PK parameters.

Secondary endpoints

Adverse event (type, frequency and intensity), Adverse Events of Special Interest (AESIs), vital signs (systolic and diastolic BP, heart rate), recorded triplicate ECG (intervals, rhythm, and morphology),

clinical chemistry, hematology, and urinalysis
Statistical methods Sample Size 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 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 [19, 22]. The sample size of eight subjects per group is also based on the feasibility to recruit subjects with severe renal impairment.
ICH/GCP The trial will be conducted in accordance with FDA guidelines [3] as well as the Declaration of Helsinki [2] and Good Clinical Practice [1].

Table 1: 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 (Section 7.2.3). 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.

1 Introduction

1.1 Background

Short bowel syndrome (SBS) is a malabsorption disorder that manifests as a collection of signs and symptoms such as diarrhea, steatorrhea, fluid and electrolyte disturbances, dehydration, malnutrition, and weight loss. Short bowel syndrome typically develops after loss of more than two-thirds of the small intestine, e.g., through surgical resection of the bowel secondary to Crohn's disease, mesenteric vascular complications, trauma or necrotizing enterocolitis. Short bowel syndrome intestinal failure (IF) is defined by the inability to maintain protein, energy, fluid, electrolyte, or micronutrient balance, and patients with SBS-IF are dependent on intravenous fluids, electrolytes and/or nutrients, together termed parenteral support (PS) [4]. Other patients present a less severe form of SBS defined as intestinal insufficiency (II), characterized by a remnant small intestine of 200 cm or less, a fecal energy excretion of more than 2.0 MJ/day, or consecutive small intestinal resections exceeding 150 cm [5]. Generally, SBS-II patients can maintain their protein and energy balance through hyperphagia, but some of them are considered as borderline IF patients with a high risk to require intermittent PS.

Following surgical resection, the remaining small intestine may undergo a process of structural and functional adaptation, which may lead to restoration of intestinal secretion and motility and to hypertrophy and hyperplasia of the mucosal surface. In patients with a preserved terminal ileum or colon in continuity, an increase in the endogenous hormonal secretion of the peptide hormones glucagon-like peptide-1 (GLP-1), GLP-2, and peptide YY (PYY) following nutrient ingestion may play a role in this adaptation. However, for patients with resection of the ileum and colon, these neuroendocrine feedback mechanisms are disrupted which may be associated with the pathophysiological traits in SBS patients such as accelerated gastrointestinal (GI) motility, hypersecretion, diminished GI blood flow, and disturbed barrier function. Together these observations have led to the development and pharmacological use of GLP-2 in the intestinal rehabilitation and treatment of SBS patients [6].

Glucagon-like peptide-2 is a 33-amino acid peptide derived from posttranslational processing of proglucagon in intestinal L-cells located primarily in the terminal ileum and colon [7, 8]. GLP-2 and GLP-2 receptor agonists act in a highly localized manner in the GI tract to enhance nutrient and fluid absorption, stimulate blood flow, increase intestinal barrier function, and inhibit gastric acid secretion and gastric emptying. One of the main biological actions of GLP-2 is organ-specific stimulation of intestinal growth through increased crypt cell proliferation and decreased apoptosis of the mucosal epithelial cells [6, 7]. Data from previous clinical trials with native GLP-2 and GLP-2 analogues have demonstrated that GLP-2 supplementation has the ability to increase crypt depth and villus height [9, 10, 11] and enhance the intestinal absorptive capacity in patients with SBS [9, 10, 11, 12].

Apraglutide is a peptide analogue of GLP-2, which is under development for the treatment of SBS. Apraglutide acts as a full agonist at the GLP-2 receptor *in vitro* with potency and selectivity comparable to native GLP-2 [8]. The structure of this peptide is designed to have a longer elimination half-life by being resistant to cleavage by dipeptidyl peptidase-4 (DPP4), the major GLP-2 peptidase. The systemic half-life in various animal species as well as in human healthy subjects is significantly prolonged compared with the native human GLP-2 (approximately 30 hours when administered subcutaneously [SC] *vs* 7 minutes for native GLP-2). Apraglutide has, in various animal models, shown

a trophic effect on the small intestine and maintained the barrier function, thus preserving the physical integrity of the intestinal mucosa.

In previous nonclinical pharmacokinetics and metabolism trials, no intact parent compound (apraglutide) was found in urine, suggesting renal elimination does not play a significant role in apraglutide removal.

Previously, apraglutide has been administered in a first-in-human trial with healthy subjects to assess safety and determine pharmacokinetic (PK) characteristics, and proved safe and well tolerated at single and repeated SC doses ranging from 2.5 mg up to 25 mg. In humans, again, no intact parent compound (apraglutide) was found in urine suggesting renal elimination does not play a significant role in apraglutide removal in humans.

1.2 Rationale

This trial is a Phase 1, non-randomized, open-label, single dose, parallel-group trial of apraglutide in subjects with severe renal impairment and subjects with normal renal function (Part 1) and in subjects with mild and moderate renal impairment (Part 2) matched for age and body weight. Details on the age and body weight matching criteria are specified in Section 4 of the protocol.

Since the metabolic pathway of apraglutide is expected to be degradation into small peptides and amino acids via catabolic pathways, similar to the catabolism for endogenous GLP-2, and in keeping with previous nonclinical and clinical pharmacokinetic trials that demonstrated no intact parent compound being recovered from the urine, it is not expected that renal impairment will have an impact on the PK of apraglutide. Therefore, a reduced, adaptive trial design will be pursued. In this trial design, only subjects with severe renal impairment and normal renal function will be studied first. In this manner, the effect of renal impairment on apraglutide PK will be initially evaluated in the renal impaired population most likely to be of impact. The impact of renal impairment expression of cytochrome P450 (CYP) enzymes, if any, is expected to be minimal and hence can also be evaluated in the severely renally impaired population to estimate degree of impact. If the trial results confirm that severe renal impairment does not alter PK to an extent that warrants dose adjustment, no further trial is warranted. If the results do not support such a conclusion, Part 2 will be conducted in subjects with moderate and mild renal impairment, based on the decision criteria outlined in Section 3.

Single-dose of SC apraglutide PK appears to be linear in the dose ranges between 2.8 mg to 56.9 mg relative to C_{max} and AUC_{inf}. No direct enzyme inhibition/induction or time-dependent enzyme inhibition is expected. The absolute bioavailability was 24.6% and the terminal half-life ($t_{1/2}$) was approximately 30 hours. Considering a linear PK at the therapeutic dose range being tested in Phase 2 trials (5–10 mg) in which single-dose PK behavior can predict multiple dose PK, a single-dose trial will be conducted to evaluate apraglutide PK under conditions of renal impairment.

The trial will use a single dose of 5 mg apraglutide administered via SC injection.

1.3 Risk-benefit Assessment

The overall conclusion from the nonclinical and Phase 1 and 2 trials conducted with apraglutide is that there are no apparent safety concerns with the administration of apraglutide in the 5 mg dose selected for this trial. A single dose of 56.9 mg was safe and well tolerated in the single ascending dose (SAD)

part of the entry into human trial. The selected dose of 5 mg is expected to produce exposures well below the levels previously found to be safe and well tolerated, even accounting for some increase in renally impaired subjects. Current data indicate that apraglutide has intestinotrophic effects on the intestinal epithelium, which may result in transient abdominal side effects.

In the following sections, the current nonclinical and clinical experience with apraglutide is summarized. A detailed review of pre-clinical and Phase 1 results is provided in the Investigator's Brochure.

1.3.1 Nonclinical Experience

1.3.1.1 Pharmacokinetics

Nonclinical trials of apraglutide have been conducted in mice, rats, monkeys and minipigs.

The PK properties of apraglutide, administered at various dose levels either intravenously (IV) as a single bolus or by SC injection, were found to be consistent across species with no apparent sex differences. The PK profile was characterized by a low systemic clearance, small volumes of distribution, and a long half-life when compared to human GLP-2 and other known GLP-2 agonists. Following SC administration, apraglutide displayed absorption-controlled kinetics resulting in a protracted half-life being 5–6 times longer compared to the half-life after IV administration. It is believed that the low clearance and the long half-life depend, at least in part, on the high protein binding and slow metabolism of the drug.

1.3.1.2 Safety

Single-, 2-week and 5-week repeated dosing trials in rats and minipigs showed dose-related mucosal effects (hyperplasia and hypertrophy of intestinal villi and crypts) of apraglutide in the intestine of both species, demonstrating the expected mode of action of the compound and the responsiveness of both animal species to the treatment.

When the intestinal mucosa was examined by standard histology, morphometry or immunohistochemistry for proliferation and apoptosis, no adverse forms of cell growth, e.g., aberrant cell division, pre-neoplastic or neoplastic changes, excessive apoptosis or cell necrosis were revealed. Moreover, additional investigation conducted *in vitro* using 50 tumor cell lines, including several colon cancer cell lines, showed that the expression of the GLP-2 receptor mRNA in the large majority of these cell lines is extremely low (100-fold to >1000-fold lower) when compared to the expression of the GLP-2 receptor mRNA of the positive controls. Therefore, the pharmacologic profile of apraglutide was found to be consistent with a minimal risk of direct action to stimulate proliferation of tumor cells or the release of growth factors from tumor cells.

Data from the pivotal toxicology *in vivo* trials (5-week repeated treatment) also indicated that apraglutide was not immunogenic in the selected animal species, had no dose-limiting or adverse systemic changes, and no effect on the respiratory, cardiovascular or nervous systems. Apraglutide did not induce genotoxicity when tested using *in vitro* or *in vivo* assays and did not have effects on reproductive organs with regard to clinical behavior, weight of the organs or macroscopic/microscopic examination.

Regarding local tolerance, investigation in the minipig found a presumably concentration-dependent local irritating potential of the dose formulations that were considered to be of human relevance. The degree of local irritation observed, however, was minimal to slight and similar to the vehicle control.

1.3.2 Clinical Experience

To date, 104 subjects participated in four clinical trials with apraglutide among whom 82 subjects (66 healthy subjects and 16 SBS patients) received at least one dose of apraglutide. These four completed clinical trials are described below:

- Two Phase 1 clinical trials in healthy subjects:
    - Clinical trial GYM-P3-698, a single-ascending dose (SAD) and multiple-ascending dose (MAD), placebo-controlled clinical trial of apraglutide in healthy adult subjects evaluating safety, tolerability, PK, and PD
    - Clinical trial TA799-002, a multiple-dose parallel arm clinical trial in healthy adult subjects to evaluate the effect of multiple SC doses of either apraglutide (1, 5, or 10 mg) or placebo once weekly for 6 weeks on the PD marker citrulline
- Two Phase 2 clinical trials designed to assess the safety and tolerability and to demonstrate proof-of-concept for apraglutide in SBS subjects:
    - Clinical trial GLY-321-2017, an open label metabolic balance clinical trial in SBS subjects testing a weekly dose of 5 mg apraglutide in SBS patients
    - Clinical trial GLY-311-2017, a dose-exploration clinical trial in SBS-IF subjects testing weekly 5 mg apraglutide against placebo and 10 mg apraglutide in an open-label extension

1.3.2.1 Pharmacokinetics

Dose-proportional PK parameters obtained by non-compartmental analysis were seen after multiple doses for apraglutide within the range of 5.7 mg to 56.9 mg in clinical trial GYM-P3-698 and within the range of 1 mg to 10 mg in clinical trial TA799-002.

A population PK/PD model of apraglutide in healthy subjects and SBS patients [13] has been developed with data provided by the 82 subjects exposed to apraglutide to date. This model describes well apraglutide concentrations across the whole-body weight range of the subjects and for the doses of 1 to 50 mg SC with one central compartment with zero-order absorption from the subcutaneous administration site and first order elimination from the central compartment. The typical PK parameters for a 70 kg-weight human receiving 5 mg are:

- Absorption duration: 1.46 days
- Apparent volume of distribution: 31.5 L
- Clearance: 16.8 L/day
- Half-life: 1.32 days

The inter-individual variability (% coefficient of variation [CV]) was 35% on clearance and 41% on the volume of distribution. Body weight influenced clearance and the volume of distribution. No

statistically significant difference was found between the PK parameters of healthy subjects and SBS patients.

Body weight was found to be a covariate on clearance and apparent volume of distribution.

1.3.2.2 Pharmacodynamics

Apraglutide increased plasma citrulline levels (a surrogate marker of small intestine enterocyte mass and function) and increased intestinal absorption as demonstrated by the following:

In clinical trials GYM-P3-698 and TA799-002, plasma citrulline levels increased in a dose dependent manner reaching a plateau at approximately 10 mg.

In the metabolic balance clinical trial GLY-321-2017, apraglutide at a weekly dose of 5 mg increased intestinal absorption after 4 weeks of treatment, as evidenced by increased wet weight absorption, energy absorption, and urinary output in SBS patients.

The results seen with apraglutide in the dose-exploration clinical trial GLY-311-2017 are consistent with those seen in the metabolic balance clinical trial GLY-321-2017. Apraglutide increased urinary output, a surrogate marker of intestinal absorption. No statistically significant difference between 5 mg and 10 mg doses was observed.

1.3.2.3 Safety

Apraglutide has been generally safe and well tolerated in the clinical studies conducted to date as demonstrated by the following:

- Doses up to 56.9 mg were safe and well tolerated in the SAD and MAD parts of the Phase 1 clinical trial GYM-P3-698
- Apraglutide was well tolerated up to six weekly doses of 10 mg in clinical trial TA799-002 in healthy subjects
- A dose relationship has not been seen for any adverse event (AE) in any of the studies
- The most frequent AEs in clinical trial GLY-321-2017 included nausea, GI stoma output decreased, and stoma complications
- Frequent AEs in clinical trial GLY-311-2017 were primarily related to the expected PD effects of apraglutide, including decreased stoma output or stoma output abnormal, polyuria, and decreased thirst
- Serious AEs (SAEs) have primarily been disease complications that are common in SBS subjects, including device-related sepsis and device malfunction. Two subjects had three treatment-emergent SAEs. All of the SAEs resolved; only one SAE, abdominal pain, was assessed by the Investigator as related to apraglutide
- For each hematology, coagulation, and chemistry parameter, mean and median change from baseline were not clinically significant. Isolated occurrences of clinically-significant, out-of-range laboratory parameters were reported as AEs, but there was no consistent pattern with the occurrence of these events
- No QTcF prolongation >500 milliseconds was seen in any of the clinical trials. In clinical trials GLY-311-2017 and GLY-321-2017, the changes from baseline in the QTcF values were

≤30 msec for all subjects at all time points, except for one subject at the EOT visit and in another subject at pre-dose of Period 3

- Low-titer anti-drug antibodies (ADA) have been seen in five subjects (none in clinical trial GYM-P3-698, one in clinical trial TA799-002, three in clinical trial GLY-311-2017, and one in clinical trial GLY-321-2017). ADA had no apparent effect on either the PD or PK of apraglutide

2 Trial Objectives and Endpoints

2.1 Objectives

2.1.1 Primary Objective

- Part 1 of clinical trial: To assess the pharmacokinetics (PK) of apraglutide in subjects with severe renal impairment compared to matched control subjects with normal renal function following single SC dose administration
- Part 2 of clinical trial (if applicable; see criteria to move to Part 2 in Section 3.1.1): To assess the PK of apraglutide in subjects with moderate and mild renal impairment compared to matched control subjects following single SC dose administration

2.1.2 Secondary Objective

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

2.2 Endpoints

2.2.1 Primary Endpoints

- Plasma apraglutide PK parameters: C_{max} and AUC_{inf}, AUC_{last}, $AUC_{0\text{-}7days}$, T_{max}, λ_z, $t_{½}$, CL/F, V_z/F
  C_{max} and AUC_{inf} or AUC_{last} are primary PK parameters. All others as secondary PK parameters

2.2.2 Secondary Endpoints

- Adverse events (type, frequency and intensity), adverse events of special interest (AESIs), vital signs (systolic and diastolic blood pressure [BP], heart rate), recorded triplicate ECG (intervals, rhythm, and morphology), clinical chemistry, hematology and urinalysis

3 Overall Design and Plan of the Trial

3.1 Overview

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 by subcutaneous injection in a clinical research unit (CRU). A staged approach as outlined 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) using the Chronic Kidney Disease Epidemiology (CKD-EPI) equation (Table 2).

Table 2: 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

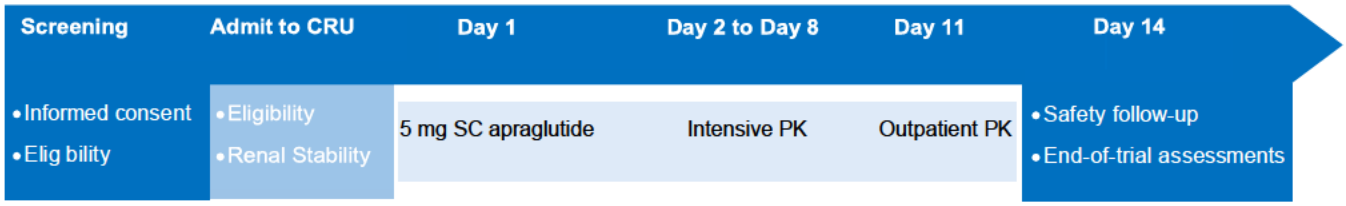
Cohort[a]	eGFR (mL/min/1.73 m^2)[b]	N
3 (Moderate Renal Impairment)	≥30 to <60	8
4 (Mild Renal Impairment)	≥60 and<90	8

a. Stages of Renal Impairment are based on the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Chronic Kidney Disease (CKD) [15].

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 [16]:
$eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [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
$\kappa = 0.7$ (females) or 0.9 (males)
$\alpha = -0.329$ (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

Figure 1: Trial Schematic



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

3.1.1 Part 1 of Clinical Trial

A total of approximately 16 subjects will be enrolled in Part1; approximately eight subjects with severe renal impairment (Cohort 1) and approximately eight 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 ±15kg of the mean of the severe renal impairment group. 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 (AUC_{inf} or AUC_{last} [if AUC_{inf} cannot be calculated]) geometric mean ratio (GMR) for the severe renal impairment group (compared to the normal group as control) is ≥2. This metric is supported by recommendations from Huang *et al* [14]. Furthermore, apraglutide was well tolerated up to 56.9 mg SC QW and very well tolerated at 28.4 mg SC QW, further demonstrating the large therapeutic margin of apraglutide. If this 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, additional subjects can be enrolled at the discretion of the sponsor.

3.1.2 Part 2 of Clinical Trial

Based on whether 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 [15]. 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 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.

3.1.3 For Both Parts 1 and 2 of Clinical Trial

All subjects in both normal and renal impairment groups will provide informed consent and undergo screening evaluations to determine their eligibility. Subject screening for participation in this trial will consist of up to two CRU outpatient visits not more than 14 days apart (but at least 3 days apart) to confirm renal stability. The first screening visit will occur within 28 days prior to administration of apraglutide. For those subjects with renal impairment, if a historical eGFR within 3 months (90 days) of Screening is not available to confirm stability, a second eGFR value will be obtained (3 to 14 days

apart). The second eGFR value may be obtained at admission, assuming the admission falls at least 3 days, but not more than 14 days following collection of eGFR value at initial screening.

The average of the two values will be utilized for subject classification. If the renal function stability criterion is met, but the renal function classification category changes between the eGFR value measured at Screening 1 visit (S1) and the calculated average of the eGFR value measured at S1 and Screening 2 visit (S2, which may be obtained at admission), then a third eGFR value may be measured at the Investigator's discretion within the screening window. The calculated average of all three eGFR values will then be utilized to determine renal function classification and subject stratification.

Each subject will be admitted to the CRU on Day -1 (at least 12 hours prior to the dose of apraglutide on Day 1) and will be confined to the CRU until Day 8.

On the morning of Day 1, the subjects will receive apraglutide as a single 5 mg SC dose after a fast of at least 8 hours. No food will be allowed for at least 2 hours post dose. Serial blood samples at specified time intervals (see Section 7) will be collected on site for up to 168 hours post dose (Day 8), prior to discharge from the CRU. A final PK sample will be collected at 240 hours (Day 11) during an outpatient visit. The average of the S1 and S2 eGFR values will be used in PK analysis. Historical eGFR within the past 3 months may be used with the S1 value for the average calculation for PK analysis, if available.

Safety assessments will be performed during S1, and on Day -1, Day 2, Discharge Day 8, and at follow-up on Day 11 and Day 14±2 days. If necessary, one serum creatinine will be additionally assessed on S2 for eGFR estimation. Physical examination, vital signs measurements, and clinical laboratory tests will be conducted and AEs will be monitored from the point of informed consent to assess safety. The total participation time (i.e., CRU confinement time for trial procedures for each subject in this trial is approximately 8 nights/9 days (excluding Screening and Follow-up visits).

Calculation of eGFR

The following CKD-EPI Creatinine Equation [16] will be used to calculate eGFR:

$$eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

Notes: eGFR is expressed as mL/min/1.73 m^2 of body surface area, SCr (serum creatinine) is expressed in mg/dL

$\kappa = 0.7$ (females) or 0.9 (males) $\alpha = -0.329$ (females) or -0.411 (males)

min = indicates the minimum of SCr/κ or 1 max = indicates the maximum of SCr/κ or 1 and age is in years

To be enrolled in the trial, subjects must demonstrate stable renal function, with ≤25% change based on either one of the following:

- Use of historical eGFR provided in source (calculated by the CKD-EPI equation) to determine ≤25% change based on comparison between historical value (within 3 months or 90 days) and Screening visit

- Based on S1 eGFR and S2 eGFR (calculated by the CKD-EPI equation). The S2 eGFR assessment should be performed between 3 and 14 days after the S1 eGFR assessment. S2 assessment can be performed at check-in on Day -1
- If the renal function stability criterion is met and the renal function classification category remains the same between history eGFR and S1 eGFR and/or the average of S1 and S2 eGFRs, subject is eligible for enrollment
- If the renal function stability criteria are not met, an additional eGFR can be performed at the Investigator's discretion. The average of all three eGFR values will be utilized for subject stratification. If a value is deemed erroneous by the Investigator, the value will be discussed with the Sponsor and a determination will be made if the value can be excluded from the average calculation
- If the renal function stability criterion is met but the renal function classification category changes between S1 eGFR and the average of S1 and S2 eGFRs (or average between historical and S1), a third eGFR value may be obtained at the Investigator's discretion within screening window, and the average of all three eGFR values will be utilized for subject stratification

3.1.4 Re-screening

In case of screen failure related to eGFR stability and/or change in the renal function classification category, subjects may be re-screened once after a 30-day period, provided that the initial screen failure is not due to an inclusion/exclusion criterion that results in permanent disqualification from enrollment (e.g., medical history). This can be done only with Sponsor's approval. A new ICF must be signed prior to any clinical trial-specific procedures for all subjects approved to re-screen.

Please see Table 3 below regarding the demonstration of stable renal function:

Table 3: Criteria to establish Stable Renal Function

Renal function Measurement	eGFR	Criterion for stability
Historical (Within 90 days) or S1	G1	
S2 (Within 3 to 14 days after S1)	G2	$\Delta=\|G2-G1\|\times100/G1$[a] If $\Delta \leq 25\%$; stable If $\Delta > 25\%$; not stable

S1= Screening Visit 1; S2= Screening Visit 2.

[a] Parenthesis of | | represents absolute values.

3.2 Drug, Route, Dosage and Treatment Plan

The therapeutic relevance of SC injections with a GLP-2 analogue for the treatment of subjects with SBS intestinal failure has recently been established [7].

In the previous first-in-human, placebo-controlled, randomized Phase 1a trial, the results of the single ascending doses and multiple doses (once a week for three consecutive weeks) found apraglutide to be generally safe and well tolerated up to the 25 mg dose since the reported AEs were only mild in severity.

Due to the long half-life of apraglutide (approximately 30 hours after SC dosing), the 25 mg dose was able to maintain a plasma concentration of apraglutide of not less than 60 ng/mL over a week. Based on literature for another GLP-2 analogue, teduglutide (GATTEX™) [12], adjusting for the high protein binding of apraglutide and a similar potency compared to teduglutide, a plasma concentration of 60 ng/mL apraglutide is expected to be efficacious.

Recent analyses of pharmacology data collected in preclinical trials applying a large range of doses suggest that a lower dose of apraglutide, such as 5 mg, could also show pharmacological activity (increase in intestinal weight) even if it covers the 60 ng/mL threshold for less than 7 days. In fact, data from animal trials suggest that the intestinotrophic effect of apraglutide could be maintained for several days following a single dose or for several weeks after a 5-week multiple dosing both in rats and minipigs. Therefore, the 5 mg QW dose, when administered SC in humans, could be sufficient for maintaining the pharmacological effect until the next dosing on Day 7.

Since single SC dose of apraglutide PK appear to be linear in the dose ranges of 2.8mg–56.9 mg relative to C_{max} and AUC_{inf}, no direct enzyme inhibition/induction or time-dependent enzyme inhibition has been identified to date in *in vitro* trials. The absolute bioavailability was 24.6% and the $t_{1/2}$ was approximately 30 hours. Considering a linear PK at the therapeutic dose range being tested in Phase 2 trials (5–10 mg), in which single dose PK behavior can predict multiple dose PK, a single dose trial will be conducted to evaluate the apraglutide PK of a single 5 mg SC injection, under conditions of renal impairment.

3.3 End of Trial Definition

A subject is considered to have completed the trial when he or she has received one investigational medicinal product (IMP) injection and has completed the confinement period and Follow up visit.

The trial will be closed when all subjects have completed Day 14±2 (end of trial visit).

4 Trial Population

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.

4.1 Inclusion Criteria

- **All Subjects**

Subjects are eligible to be included in the trial only if all of the following criteria apply:

Age and Sex

1. Male or female subjects who are between the ages of 18–75 years, inclusive, at Screening

Type of Subject and Disease Characteristics

2. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other trial procedures
3. Body mass index (BMI) of ≥17.5 to ≤40 kg/m^2; and a total body weight of >50 kg (110 lb)
4. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol
5. Women of childbearing potential must agree to practice effective contraception and to use a highly effective method of contraception during the trial and for 1 month after the EOT visit. Such methods include: combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner. To be considered sterilized or infertile, females must have undergone surgical sterilization (bilateral tubectomy, hysterectomy, or bilateral ovariectomy) or be postmenopausal (defined as at least 12 months amenorrhea; it may be confirmed with follicle-stimulating hormone test if there is doubt and/or the woman is under 60 years of age and not using hormonal contraception or hormone replacement therapy (HRT)
6. Male subjects with a female partner of childbearing potential must commit to practice highly effective methods of contraception (e.g., condom) and abstain from sperm donation during the trial and for 1 month after the EOT visit

- **Additional Inclusion criteria for Healthy Subjects with Normal Renal Function (Cohort 2 only)**

7. No clinically relevant abnormalities identified by detailed medical history, full physical examination, including body temperature, blood pressure (BP), and heart rate measurement, 12-lead electrocardiogram (ECG), and clinical laboratory tests
8. Normal renal function (average eGFR measured by CKD-EPI ≥90 mL/min/1.73 m^2) at two screening visits where Screening 2 can be performed at admission on Day -1
9. Demographically comparable to the group of subjects with impaired renal function:
   a. That each subject's age within ±10 years of the mean age and ±15 kg of the severe renal impairment cohort (Cohort 1)

b. Attempts will be made to ensure that the male-to-female composition of Cohort 2 is comparable to that in the severe renal impairment cohort (Cohort 1)
c. Other demographic characteristics such as race and ethnicity matched as closely as possible to the renal impairment cohort

➢ **Additional Inclusion criteria for Subjects with Impaired Renal function (Cohort 1 and Cohorts 3 and 4 [if applicable] only)**

10. Good general health commensurate with the population with chronic kidney disease (renal impairment). "Health" is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, measurement of heart rate and 12-lead ECG, as well as clinical laboratory tests (except serum creatinine and eGFR). Hypertension, diabetes mellitus, hyperparathyroidism, ischemic heart disease and other common co-morbidities in this population are possible exemptions, as long as, in the opinion of the Investigator, the subject is medically stable, is on a stable drug regimen, and can abide by the meals and dietary restrictions outlined in Section 4.3
11. Meet the following eGFR criteria (based on average) during the screening period based on the CKD-EPI equation.
    a. Severe renal impairment: eGFR <30 mL/min/1.73 m^2, but not requiring hemodialysis
    b. Moderate renal impairment (Part 2 only): eGFR ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2
    c. Mild renal impairment (Part 2 only): eGFR ≥60 and <90 mL/min/1.73 m^2

    The eGFR values obtained during Screening visits should not be more than 25% different for Cohort 1 (severe), Cohort 3 (moderate), and Cohort 4 (mild)
12. Any form of renal impairment except acute nephritic syndrome or nephrotic syndrome defined as proteinuria >3 g (subjects with history of previous nephritic syndrome but in remission can be included)
13. Stable concomitant drug regimen (as defined in Section 6.2) for the management of individual subject's medical conditions

4.2 Exclusion Criteria

➢ **All Subjects**

Subjects excluded from the trial if any of the following criteria apply:

Medical Conditions

1. Renal transplant recipients
2. History of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the Investigator within 3 months prior to Screening and Day 1
3. Any active malignancies or history of malignancies within the past 2 years prior to screening with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma *in situ*
4. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation, or behavior that may increase the risk associated with trial participation or investigational medicinal product (IMP) administration or may interfere with

the interpretation of trial results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this trial

5. Treatment with an IMP within 30 days or five half-lives, if known, (whichever is longer) preceding the dose of IMP
6. Male subjects who are unable to comply with the following requirements during the intervention period and up to 1 month after the dose of apraglutide, which corresponds to the time needed to eliminate trial interventions:
   a. Refrain from donating sperm
   b. PLUS, either be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle abstinent on a long-term persistent basis and agree to remain abstinent
   c. OR must agree to use a male condom with spermicide when engaging in any activity that allows for passage of ejaculate to another person
   d. Vasectomy
7. A history of clinically significant intestinal adhesions and/or chronic abdominal pain
8. History of known colon polyps or family history of familial adenomatous polyposis

Diagnostic Assessments

9. Positive blood screen for hepatitis C antibody, hepatitis B surface antigen or human immunodeficiency virus (HIV)-1 and -2 antibodies
10. ANY of the following abnormalities in clinical laboratory tests at Screening, and confirmed by a single repeat, if deemed necessary:
    a. Serum albumin concentration <25 g/L (2.5 g/dL)
    b. Hemoglobin concentration <90 g/L (9.0 g/dL)
    c. Enzymes aspartate amino transaminase (AST) or alanine amino transaminase (ALT) values >2 × upper limit of normal (ULN)
    d. Proteinuria of >3 g total bilirubin >1.5 × ULN; subjects with Gilbert's syndrome would be eligible for this trial provided the direct bilirubin is ≤ULN
11. In the opinion of the Investigator (or designee), subjects have any clinically significant laboratory abnormality that could affect interpretation of trial data or the subject's participation in the trial. Screening laboratory tests with abnormal results may be repeated once to confirm abnormal results (with the same screening number); the last value will be used to determine eligibility
12. Positive urine test for alcohol or illicit drugs at either Screening or admission. Renal impairment subjects may be eligible to participate after approval from Sponsor if their drug screen is positive for a prescribed substance that is not expected to interfere with the PK of apraglutide
13. Screening 12-lead ECG in triplicate that demonstrates:
    a. Clinically significant abnormalities requiring treatment (e.g., acute myocardial infarction, serious tachy- or brady-arrhythmias) or indicating serious underlying heart disease (e.g., cardiomyopathy, Wolff-Parkinson–White syndrome)
    b. Confirmed QT interval corrected using Frederica's correction factor (QTcF) >450 msec for subjects with normal renal function and >480 msec for subjects with impaired renal function
    c. Long QT Syndrome, a family history of Long QT Syndrome, or a history of Torsades de Pointes

Prior/Concomitant Therapy

14. Use of prescription or non-prescription drugs and dietary supplements within 7 days or five half-lives (whichever is longer) prior to Day 1.
    Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the trial may be permitted on a case by case basis following approval by the Investigator in consultation with the Sponsor.
    Herbal supplements must be discontinued at least 28 days prior to the dose of IMP.
    For subjects with renal impairment, stable concomitant medications (including herbal supplements) may be given if they are considered necessary for the welfare of the subjects (e.g., standard therapy for underlying diseases), and are not contraindicated with the IMP or likely to interfere with the PK of the IMP. Stable is defined as no changes in current medications or starting new medications for 14 days prior to apraglutide administration

Other Exclusion Criteria

15. Investigator site staff members directly involved in the conduct of the trial and their family members, or any site staff members otherwise supervised by the Investigator
16. History of regular alcohol consumption exceeding seven drinks/week for females or 14 drinks/week for males (1 drink = 5 ounces [150 mL] of wine, or 12 ounces [360 mL] of beer, or 1.5 ounces [45 mL] of hard liquor) within 3 months of Screening
17. Female subjects of childbearing potential who are unwilling or unable to use highly effective methods of contraception as outlined in the protocol for the duration of the trial and for at least 1 month after the administration of the IMP; pregnant female subjects; female subjects planning to become pregnant during the duration of the trial and until 1 month after the administration of the IMP; breastfeeding female subjects
18. Blood donation of approximately 1 pint (500 mL) or more within 60 days prior to the dose of IMP. Plasma donations of approximately 1 pint (500 mL) or more within 28 days prior to the dose of IMP
19. History of sensitivity to heparin or heparin-induced thrombocytopenia, *only if* heparin is used to flush intravenous (IV) catheters used during serial blood collections
20. Unwilling or unable to comply with the Lifestyle Considerations outlined in Section 4.3

- **Additional Exclusion Criteria for Healthy Subjects with Normal Renal Function (Cohort 2 only)**

21. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing)
22. Evidence or history of clinically significant dermatological condition (in the opinion of the Investigator) or visible rash present during physical examination

- **Additional Exclusion Criteria for Subjects with Impaired Renal Function (Cohort 1 and Cohorts 3 and 4 [if applicable] only)**

23. Subjects requiring hemodialysis and/or peritoneal dialysis

24. Subjects with other clinically significant disease that may affect the safety of the subject or that may affect the PK of apraglutide (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing)
25. Subjects with any significant hepatic, cardiac, or pulmonary disease or subjects who are clinically nephrotic. Hypertension, diabetes mellitus, hyperparathyroidism, ischemic heart disease, etc. are not cause for exclusion as long as, in the opinion of the Investigator, the subject is medically stable and any drugs that are administered for these conditions are not expected to interfere with the PK of apraglutide
26. Screening BP ≥180 mmHg (systolic) or ≥110 mmHg (diastolic), following at least 5 minutes of supine rest. If initial BP is ≥180 mmHg (systolic) or ≥110 mmHg (diastolic), the BP should be repeated two more times and the average of the three BP values should be used to determine the subject's eligibility. An additional set of vital signs can be obtained at the discretion of the Investigator

4.3 Lifestyle Considerations

The following guidelines are provided:

4.3.1 Meals and Dietary Restrictions

- Water is permitted without restriction during trial participation
- Subjects must abstain from all food and drink (except water) at least 8 hours prior to any safety laboratory evaluations and 8 hours prior to IMP administration on Day 1, and for 2 hours following dosing. There will be no restriction to breakfast on the other days provided other restrictions are followed
- Breakfast, lunch, and dinner can be scheduled according to the schedule at the CRU. An evening snack may be permitted prior to the start of the 8-hour fast before IMP dosing on Day 1

4.3.2 Caffeine, Alcohol, and Tobacco

- Subjects will abstain from caffeine-containing products for 24 hours prior to dosing until collection of the final PK blood sample. Subjects will additionally abstain from caffeine-containing products at least 2 hours prior to any scheduled vital signs, and ECG measurements
- Subjects will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK blood sample. Subjects may undergo a urine alcohol test at the discretion of the Investigator
- Subjects are allowed to smoke ≤5 cigarettes per day during the trial. Smoking will be monitored by the CRU

4.3.3 Activity

- Subjects will abstain from strenuous exercise (e.g., heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests and during confinement. Walking at a normal pace will be permitted
- In order to standardize the conditions on PK sampling days, subjects will be required to refrain from lying down (except when required for BP, heart rate, and ECG measurements), eating, and drinking beverages other than water during the first 2 hours after dosing

4.3.4 Contraception and Definition of Woman of Child-bearing Potential

4.3.4.1 Definition of Woman of Child-bearing Potential

- The Investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject from the permitted list of contraception methods noted below and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Assessments, the Investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly
- A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below)
- If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of trial intervention, additional evaluation should be considered

Women in the following categories are not considered women of child-bearing potential (WOCBP):

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining trial entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the subject's medical record for the trial.

3. Postmenopausal female:
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause
   - A high follicle-stimulating hormone (FSH) level in the postmenopausal range will be used to confirm a postmenopausal state in women who are less than 60 years old and not using hormonal contraception or HRT

4.3.4.2 Contraception Methods

Highly Effective Methods That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner. Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has

been confirmed. If not, an additional highly effective method of contraception should be used (e.g., male condom with spermicide). The spermatogenesis cycle is approximately 90 days

Highly Effective Methods That Are User-Dependent:

Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

- Oral
- Intravaginal
- Transdermal
- Injectable

Progestogen-only hormone contraception associated with inhibition of ovulation:

- Oral
- Injectable

Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.

5 Premature Discontinuation of Subjects or Trial

5.1 Subject Discontinuation

The subjects have the right to withdraw from the trial at any time and for any reason, without the need to justify their decision and without prejudice to their current or future medical care by the investigator or hospital.

If the reason for withdrawal is an AE, the AE should be reported and the subject should be followed up as outlined in the protocol.

Withdrawn subjects who have been dosed with the IMP must have an early termination (ET) visit performed as soon as possible after the dose for safety assessments. Regardless of the reason for withdrawal, the Investigator will make every effort to ensure an ET visit is performed for subjects who have been dosed with IMP.

The Investigator also has the right to discontinue subjects at any time based on the best interest of subjects.

Reasons for withdrawal from the trial:

- Withdrawal of consent
- Important protocol deviation that, in the opinion of the Investigator and after discussion with the Sponsor, may invalidate the trial results
- Investigator's decision for medical or safety reasons
- Pregnancy occurring between ICF signature and dosing
- Adverse events that might place the subject at unacceptable risk if participation is continued
- Subject is lost to follow-up
- The clinical trial is terminated by the Sponsor

A subject may be withdrawn if he/she develops an AESI such as hypotension, fluid overload, persistent abdominal pain, gall bladder, biliary and pancreatic disease of Grade 3 and above, according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5 [17].

Furthermore, during the trial liver toxicity will be closely monitored according to guidelines from the USA Food and Drug Administration (FDA) and subjects will be withdrawn from the trial if any of the following stopping criteria are met. Further enrolment and dosing will be interrupted if a single subject experiences documented liver function abnormalities that meet the following criteria (see also Section 10.10):

- ALT or AST >8 × ULN once
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN **and** total bilirubin >2 × ULN or INR >1.5
- ALT or AST >3 × ULN and clinical signs of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Study enrollment may potentially be resumed following the review of all available safety data by the investigator and Institutional Review Board/Independent Ethics Committee, with a concurrent/consensus opinion that the totality of the data suggests that this event is unlikely to be related to the study drug.

For all withdrawn subjects, site will attempt to perform EOT assessments matching the Day 14 visit at an ET Visit. The Investigator will document the date of discontinuation and, if possible, the main reason for the subject's withdrawal in the subject's medical record.

5.2 Subject Withdrawal of Consent and Subjects Considered Lost to Follow-up

Subjects who request to discontinue receipt of trial treatment will remain in the trial and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is only from further receipt of IMP or also from trial procedures and/or posttreatment trial follow-up, and entered on the appropriate case report form page.

All reasonable efforts must be made to locate withdrawn subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. All attempts should be documented in the subject's medical record. For subject who are lost to follow-up (e.g., have not completed the trial, but cannot be reached), the site will use legally permissible methods to determine of the subject has died and to obtain the date and cause of death (for example, through use of public domain information or a release signed by the family to obtain health records). If the Investigator uses a third-party representative to assist in the follow-up portion of the trial and that has been included in the subject's informed consent, the Investigator may use those means to access follow-up. The Investigator can also use other public vital status data necessary to complete the follow-up portion of the trial if necessary. If after all attempts, the subject remains lost to follow-up, then the last-known-alive date, as determined by the Investigator, should be reported and documented in the subject's medical record.

Subject's may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, as noted in the protocol or for behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of trial visits or procedures at a given Investigator site. The ET visit applies only to subjects who are randomized and then are prematurely withdrawn from the trial.

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as feasible following the decision to withdraw from the trial.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as a protocol deviation so long as subject safety was preserved.

If the subject withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

Subjects who withdraw from the trial may be replaced at the discretion of the Investigator upon discussion with the Sponsor.

5.3 Trial Termination

If the Investigator, the Sponsor, or the Safety Medical Monitor (who reviews medical information and safety data, and consults with the site on eligibility criteria) becomes aware of conditions or events that suggest a possible hazard to subjects if the trial continues, the trial may be terminated after appropriate consultation between the relevant parties. The trial may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant or unacceptable risk to the subjects enrolled in the trial
- Failure of the site to enroll subjects at an acceptable rate
- A decision on the part of the Sponsor to suspend or discontinue development of the drug
- The site cannot comply with the requirements of the protocol
- It is not possible for the site to comply with GCP standards
- IRB or a regulatory decision
- Enrollment and further dosing of new subjects will be interrupted if two or more subjects experience any of the AESIs mentioned in Section 5.1. of moderate intensity (NCI-CTCAE Grade 3) and/or if one or more subjects experience a Grade 4 event (unless clearly not attributable to the study drug)

6 Investigational Medicinal Product and Concomitant Medications

6.1 Investigational Medicinal Product

6.1.1 Investigational Medicinal Product Description

The IMP tested in this trial is apraglutide, a GLP-2 analogue composed of 33 amino acids, containing natural and unnatural amino acids from non-animal origin. Apraglutide is manufactured by solid-phase peptide synthesis using 9-fluorenylmethyloxycarbonyl as an amine-protecting group. The formulation of apraglutide is an aseptically manufactured freeze-dried powder for reconstitution with commercially available sterile water for injection. The content of the formulation is shown in Table 4. All the excipients are well-known pharmaceutical excipients.

Apraglutide will be supplied in vials with 12.5 mg freeze-dried powder for reconstitution in sterile water (to achieve an extractable dose of up to 10 mg) prior to SC injection.

6.1.2 Dosing and Administration

A single 5 mg dose of apraglutide will be administered by SC injection once into the abdomen on Day 1 of confinement. Detailed instructions will be provided in the IMP Manual.

The Investigator will be responsible for the preparation and administration of the IMP but can delegate this task to trained site staff.

No apraglutide will be administered to any person not enrolled in this trial.

6.1.3 Drug Accountability

The Investigator is responsible for maintaining records of all IMP and Water For Injection (WFI) vials, received, administered, and dispensed.

6.1.4 Reconstitution of Investigational Medicinal Product

Reconstitution and preparation of the solution for SC administration will be performed using aseptic techniques following all applicable guidelines. Drug handling guidelines detailing specific instructions, will be made available in the IMP Manual that will be provided to the site.

For reconstitution, sterile water will be injected into the vial to obtain a sterile solution (Table 4). The vial will be gently swirled until its contents are completely dissolved and the contents of the vial verified to be free of foreign particles.

Table 4: Reconstitution of Investigational Medicinal Product

	5.0 mg IMP
Vial content (apraglutide)	12.5 mg
Reconstitution with water for injection	0.5 mL
Volume administered	0.2 mL (=5 mg)
Concentration of reconstituted solution	25 mg/mL

After reconstitution, the apraglutide must be injected within 1 hour maximum. Timing of preparation and administration must be documented in the source and electronic case report form (eCRF).

The solution can be drawn up into the syringe immediately following reconstitution and kept at room temperature until administration or the syringe can be drawn up just before administration. The required amount of reconstituted apraglutide (0.2 mL for 5 mg) will be withdrawn from the vial into the syringe for SC injection. After drawing up the syringe, it will be inspected for foreign particles and used if judged acceptable for administration.

6.1.5 Packaging, Labelling, and Storage

Packaging and labelling of the IMP is performed by the Clinical Trial Supplies (CTS) vendor in accordance with GMP and applicable regulatory requirements.

The freeze-dried apraglutide powder is filled in 2 mL vials, sealed with rubber stoppers and aluminium caps. IMP individual vials will be labelled according to EudraLex Volume 4, Annex 13 [18] and national regulatory requirements.

The Investigator must ensure that the IMP is stored refrigerated between 2–8°C in a secure location with controlled access. At the site, the temperature will be continuously monitored and the electronic log must be checked once daily during working days. Temperature deviations outside the allowed range must be reported and evaluated prior to use of the apraglutide. Details will be provided to the site in the IMP Manual.

6.2 Concomitant Medications

6.2.1 Previous and Concomitant Medication

Concomitant medication is any medication apart from the IMP that is used during the subject's participation in the trial. All concomitant medication used, including vitamins and mineral supplements, must be recorded from the time of signature of the ICF to the end of the trial. The Investigator or delegate must seek information on concomitant medication use at each trial visit. The information collected for concomitant medication must include:

- Medication name (preferably generic name)
- Indication
- Dosage
- Frequency
- Route of administration
- Start and stop date or continuation

6.2.2 Prohibited Previous and Concomitant Medication

Any use of growth hormone, glutamine or growth factors such as GLP-1, GLP-2 or analogues thereof is prohibited within the last 3 months prior to Screening and throughout the trial.

Systemic corticosteroids, methotrexate, cyclosporine, tacrolimus, sirolimus, infliximab or other biologic therapy/immune modifiers are prohibited within 30 days of Screening and throughout the trial.

Use of prescription or non-prescription drugs and dietary and herbal supplements are prohibited within 28 days or five half-lives, if known, (whichever is longer) prior to the first dose of IMP unless deemed necessary by the Investigator for the treatment of concurrent disease consistent with subjects with renal impairment.

Acetaminophen may be used at doses of ≤3 g/day.

No new medication should be started during the trial, unless medically necessary and prescribed by the Investigator or another qualified designee involved in the subject's care and being aware of the subject's participation in the trial.

All concomitant treatments taken during the trial must be recorded with indication, daily dose, and start and stop dates of administration. Concomitant drug and non-drug treatment will be collected. All subjects will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of IMP will be documented as a prior treatment. Treatments taken after the first dose of IMP will be documented as concomitant treatments.

6.2.2.1 Subjects with Healthy Renal Function (Cohort 2 only)

In general, subjects will abstain for all concomitant treatments (prescription or over the counter) as described in the Section 4.2, except for the treatment of AEs.

6.2.2.2 Subjects with Impaired Renal Function (Cohort 1 and Cohort 3 and 4 [if applicable])

Subjects are permitted to be on stable doses (defined as no changes in current medications or new medications within 14 days prior to apraglutide administration) of background medications if they are considered necessary for the welfare of the trial subjects (e.g., standard therapy for the underlying disease), are not contraindicated with the IMP, and are unlikely to interfere with the PK of the IMP. ***Whenever possible***, attempts must be made to ***not*** alter the doses and regimens of the concomitant medications after Day 1 and until the EOT on Day 14±2 days.

7 Trial Schedule and Assessments

7.1 Screening Visit

Screening Visit 1

Subjects will be screened within 28 days prior to administration of the IMP to confirm that they meet the subject selection criteria for the trial. The Investigator (or designee) will obtain informed consent from each subject in accordance ICH/GCP guidelines. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (e.g., delayed drug shipment), then subjects do not require rescreening if the Day -1 laboratory results meet eligibility criteria. Maximum delay accepted between screening and IMP administration is a total of 42 days.

Subjects who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided the Day -1 laboratory results meet the eligibility criteria for this trial within 1 month after the date of screening.

The following procedures will be completed (Table 1):

- Obtain written informed consent
- Confirm and document that the subject meets the inclusion/exclusion criteria
- The Investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the contraception guidelines and will confirm highly-effective, proper contraception is being used
- Collect demography (subject race, ethnicity, date of birth, age, sex)
- Collect height and weight and calculate BMI
- Obtain medical history, including history of prior illegal drug, alcohol and tobacco use
- Obtain complete medication history for all prescription or non-prescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned dose
- Obtain a supine BP and heart rate after at least 5 minutes of rest in a supine position. One repeat measurement may be allowed at the discretion of the investigator
- Obtain body temperature
- Conduct a full physical examination (PE); this must be performed by trained medical personnel at the CRU
- Collect 12-lead ECG in triplicate after supine rest of 10 minutes or per CRU standard operating procedure
- Assess baseline symptoms/AEs
- If applicable, obtain as source document, prior/historical eGFR from the past 3 months using CKD-EPI equation (for Cohorts 1 [severe], 3 [moderate] and 4 [mild] only)
- Collect blood and urine specimens for the following:
    - Safety laboratory tests (hematology, clinical chemistry and urinalysis)
    - Urine drug or alcohol test
    - Serum follicle-stimulating hormone concentration for any female subject who has been amenorrhoeic for at least 12 consecutive months and is under 60 years of age; serum pregnancy test for any woman of child bearing potential

- Collect blood for HIV, HBsAg, HBcAb, and HCV core Ab testing
- Serum creatinine and eGFR calculation using CKD-EPI equation
- An optional glycosylated hemoglobin (HbA1c) and thyroid stimulating hormone (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)

- To prepare for trial participation, subjects will be instructed on all pertinent lifestyle requirements and restrictions

Screening visit 2 (if applicable)

- If no historical serum creatinine/eGFR using CKD-EPI is available within the past 3 months (90 days), the subject will be asked to return to the CRU at least 72 hours but no more than 14 days following initial collection of eGFR for Screening 2 for the determination of serum creatinine/eGFR using CKD-EPI and confirmation of renal stability alone (for Cohorts 1 [severe], 3 [moderate], and 4 [mild] only). This second eGFR value may be obtained at admission
- Weight
- Contraception check
- Concomitant medication
- Adverse event/SAE monitoring

7.2 Safety Assessments

Every effort should be made to ensure that protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator must take all steps necessary to ensure subject safety. When a protocol-required test cannot be performed, the Investigator will document the reason in the source documents for the missed test. This will be reported as a protocol deviation. Corrective and preventative actions will be discussed with the site by the Monitor to ensure that required processes are adhered to, as soon as possible.

For samples being collected and shipped, detailed collection, processing, storage and shipment instructions and contact information will be provided to the Investigator's site prior to initiation of the Trial.

7.2.1 Laboratory Tests

The following safety laboratory tests (Table 5, Table 6) will be performed at times defined in the trial procedures section of this protocol (Table 1). Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from a calculated value. These additional tests would not require additional collection of blood. Unscheduled laboratory measures may be obtained at any time during the trial to assess a perceived safety concern and updated rationale and outcome documented in the source documents.

Table 5: Sampled Blood Volume

Type	Volume per sample (mL)	Sample number	Total (mL)
Serology	6.5	1	6.5
Hematology	3	6	18
Chemistry	7	6	42
Thyroid-stimulating hormone (not additional if added to Chemistry panel)	3.5	1	3.5
Glycosylated hemoglobin	3	1	3
Pharmacokinetic samples	3	30	90
Total			**163 mL**

Table 6: Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN	pH	TSH
Hematocrit	Creatinine	Glucose (qualitative)	HbA1c
RBC count	Glucose (fasting)	Protein (qualitative)	FSH[b]
MCV	Calcium	Blood (qualitative)	Urine drug test
MCH	Sodium	Ketones	Urine alcohol test
MCHC	Potassium	Nitrites	Serum pregnancy test
Platelet count	Chloride	Leukocyte esterase	(β-hCG)
WBC COUNT	Total CO_2	Urobilinogen	eGFR
Total neutrophils (%, Abs)	AST, ALT	Urine bilirubin	HBsAg[c]
Eosinophils (%, Abs)	Total bilirubin	Specific Gravity	HBcAb[c]
Monocytes (%, Abs)	ALP	Microscopy[a]	HCV core antibody[c]
Basophils (%, Abs)	Uric acid		HIV -1, -2[c]
Lymphocytes (%, Abs)	Albumin		
	Total protein		
	Lipase		
	Amylase		
	Magnesium		
	Phosphate		
	Ferritin		
	Lactate dehydrogenase		
	C reactive protein		
	Additional Tests (Needed for Hy's Law)		
	AST, ALT (repeat)		
	Total bilirubin (repeat)		
	Albumin (repeat)		
	ALP (repeat)		
	Direct bilirubin		
	Indirect bilirubin		
	CK		
	GGT		
	PT/INR		
	Total bile acids		

[a] Only if urine dipstick is positive for blood protein, nitrites or leukocyte esterase.

[b] At Screening only, in females who are amenorrhoeic for at least 12 consecutive months who are less than 60 years old and not using hormonal contraception or hormone replacement therapy.

[c] At Screening only.

The total blood volume drawn will be approximately 163 mL per subject. Additional samples may be added if any laboratory result is outside of the normal range or for safety purposes. The samples will be destroyed after analysis.

The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol, opiates/opioids, benzodiazepines and amphetamines. Additional drugs of abuse screening that is part of the CRU protocol (on-site drug screen) will also be allowed. Subjects may undergo random urine drug testing at the discretion of the Investigator.

Subjects will also be tested for alcohol in urine samples.

7.2.2 Physical Examinations

A complete physical examination (PE) will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and basic neurological systems.

An abbreviated PE will include, at a minimum, assessments of general appearance, the respiratory, abdominal, and cardiovascular systems, and subject-reported symptoms.

Symptom-directed PE can be performed at the discretion of the Investigator at any time if clinically indicated.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the protocol. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

7.2.3 Vital Signs

Supine BP will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mmHg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the trial. Every effort should be made to utilize the same method of measurement during the trial (automated versus manual). Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. Any repeat vital signs measurement will be taken manually. The use of an automated device for measuring BP and heart rate is acceptable; however, when done manually, heart rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and heart rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and heart rate will be permitted, as necessary, to ensure appropriate collection of safety data.

In some cases, it may be appropriate to repeat abnormal vital signs to rule out measurement errors due to e.g., improperly placed BP measurement cuff.

Temperature will be measured using non-contact temperature assessment devices. No eating, drinking, or smoking is allowed for 10 minutes prior to the measurement.

7.2.4 Twelve-lead Electrocardiogram

Twelve-lead ECG will be performed in triplicate in a consecutive manner after the subject has been resting in the supine position for at least 10 minutes. The readings should be at least 1 minute apart. The average value of the triplicate ECG will be collected for inclusion criteria for the QTcF. The ECGs in this manner should be collected at times specified in this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc and QTcF intervals and QRS complex.

To ensure safety of the subjects, a qualified individual at the Investigator site will make comparisons to baseline measurements (pre-dose on Day 1). Additional ECG monitoring will occur if a) a post-dose QTc interval remains ≥30 msec from the baseline or an absolute QTc value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then two additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTc values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from two successive ECGs fall below the threshold value that triggered the repeat measurement.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range using calipers.

Triplicate ECG recordings should be performed before vital signs and laboratory blood collections at the same time point.

A paper or digital copy of the ECG should be filed in the subject's chart and must be available to the Sponsor upon request. Any clinically significant changes will be recorded and evaluated further, as clinically warranted.

7.2.5 Clinical Safety Laboratory Assessments

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the eCRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the trial should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or the Safety Medical Monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the schedule of those assessments per protocol.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

Subjects may undergo random urine drug testing at the discretion of the Investigator.

7.2.6 Pregnancy and Confirmation of Postmenopausal Status

Pregnancy tests will be serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the schedule of the assessments (Table 1). Women of child-bearing potential must be using a permitted contraceptive method to be eligible for trial participation. Following a negative pregnancy test result at Screening, appropriate contraception must be commenced, and a second negative pregnancy test result will be required at the baseline visit prior the subject's receiving the IMP. Pregnancy tests will also be done whenever a menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the trial. Pregnancy tests may also be repeated if requested by IRBs or if required by local regulations.

An FSH test will also be performed on any woman who is not of child-bearing potential on the basis of amenorrhea for a consecutive 12-month period who is less than 60 years old and not using hormonal contraception or HRT.

7.2.7 Injection Site Reaction Assessments

Subjects will be assessed for any injection site reaction related to apraglutide administration. This will include the following: bleeding, bruising, redness, tenderness, swelling, rash, discharge, and temperature. Any injection site reactions deemed by the Investigator will be documented as AEs.

7.3 Trial Procedures at Each Visit

For the trial period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing; the following chronology of events should be adhered to, where possible.

- Electrocardiogram in triplicate: obtain prior to vital signs measurements after a 10-minute supine rest and as close as possible to the scheduled time, but prior to blood specimen collection
- Vital Signs: obtain BP/heart rate as close as possible to scheduled time, but prior to blood specimen collection and after 5 minutes of supine rest; body temperature will be taken using a non-contact assessment device
- Pharmacokinetic blood specimens
- Other procedures: obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection

7.3.1 Day -1

Subjects will be admitted to the CRU on Day -1 prior to Day 1 dosing. The following procedures will be completed following admission to the CRU:

- Review of inclusion and exclusion criteria.
- Obtain blood and urine samples for safety laboratory tests (hematology, clinical chemistry, urinalysis) after 8 hours fast. The results must have no clinically significant findings as judged

by the investigator, in order for a subject to be given IMP on Day 1. A serum pregnancy test for any WOCBP
- Measure weight
- Collection of urine for drug screen and alcohol test. These tests may be performed at any other time at the discretion of the Investigator
- The Investigator or his/her designee will discuss with subjects the need to use highly effective contraception consistently and correctly according to the contraception guidelines and will confirm highly effective contraception is being used
- Serum creatinine, eGFR calculation using CKD-EPI
- Collect 12- lead ECG in triplicate after supine rest of 10 minutes or per CRU standard operating procedure
- Obtain supine BP and heart rate after at least 5 minutes of rest in a supine position. One repeat measurement may be allowed at the discretion of the Investigator
- Obtain body temperature
- Assess baseline symptoms/AEs
- Review prior and concomitant medication(s)
- Review changes in subject's medical history, including medication history since Screening
- Conduct a complete PE only when a complete PE was not performed at S1 visit. If a complete PE was performed at screening visit, an abbreviated PE will be done at this point
- Begin overnight fasting (8 hours) prior to Day 1 dose

7.3.2 Day 1

Prior to apraglutide dosing, the following procedures will be completed.

- Injection Site Assessment
- Assess baseline symptoms/AEs
- Collect 12 lead triplicate ECG measurements within 45 minutes of dosing
- Collect supine BP/heart rate, and body temperature within 45 minutes of dosing
- Collect blood sample for PK analysis of apraglutide at approximately 5 minutes pre-dose

Dosing

- Dosing with 5 mg SC apraglutide will be given in the abdomen of the trial subject at time zero by the Investigator or qualified/trained designee

After dosing, the following procedures will be completed:

- Collect 12-lead triplicate ECG measurements at approximately 4 hours post-dose
- Assess supine BP/heart rate and body temperature at 1 and 4 hours post-dose
- Collect blood samples for PK analysis at 6 and 12 hours post-dose on Day 1
- Review concomitant treatments
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "Have you noticed any changes to your physical condition?"
- Injection site reaction assessment at approximately 4 hours post-dose

7.3.3 Day 2

The following procedures will be completed:

- Assess supine BP/heart rate and body temperature approximately 24 hours after dosing on Day 1
- Collect triplicate ECG at approximately 24 hours post-dose
- Collect blood and urine samples for safety laboratory tests (hematology, clinical chemistry, urinalysis) 24 hours after dosing on Day 1
- Collect blood samples for PK analysis of apraglutide at 24, 28, 36, and 40 hours after dosing on Day 1
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "Have you noticed any changes to your physical condition?"
- Review concomitant treatments
- Injection site assessment at approximately 24 hours post-dose

7.3.4 Day 3

The following procedures will be completed:

- Assess supine BP/heart rate and body temperature approximately 48 hours after dosing on Day 1
- Collect blood samples for PK analysis of apraglutide at 48 and 60 hours after dosing on Day 1
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "Have you noticed any changes to your physical condition?"
- Review concomitant treatments
- Symptom-driven PE, if indicated, to be performed by the Investigator or trained medical professional/designee
- Injection site reaction assessment at approximately 48 hours post-dose

7.3.5 Day 4

The following procedures will be completed:

- Assess supine BP/heart rate and body temperature approximately 72 hours after dosing on Day 1
- Collect blood samples for PK analysis of apraglutide at 72 hours after dosing on Day 1
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "Have you noticed any changes to your physical condition?"
- Review concomitant treatments
- Injection site assessment at approximately 72 hours post-dose

7.3.6 Day 5

The following procedures will be completed:

- Assess supine BP/heart rate and body temperature approximately 96 hours after dosing on Day 1
- Collect blood samples for PK analysis of apraglutide at 96 hours after dosing on Day 1

- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "Have you noticed any changes to your physical condition?"
- Review concomitant treatments
- Injection site assessment at approximately 96 hours post-dose

7.3.7 Day 6

The following procedures will be completed:

- Assess supine BP/heart rate and body temperature approximately 120 hours after dosing on Day 1
- Collect blood samples for PK analysis of apraglutide at 120 hours after dosing on Day 1
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "Have you noticed any changes to your physical condition?"
- Review concomitant treatments
- Injection site assessment at approximately 120 hours post-dose

7.3.8 Day 7

The following procedures will be completed:

- Assess supine BP/heart rate and body temperature approximately 144 hours after dosing on Day 1
- Collect blood samples for PK analysis of apraglutide at 144 hours after dosing on Day 1
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "Have you noticed any changes to your physical condition?"
- Review concomitant treatments
- Injection site assessment at approximately 144 hours post-dose

7.3.9 Day 8

Subjects may be discharged from the CRU after completion of assessments. The following procedures will be completed 168 hours after apraglutide dosing on Day 1:

- Abbreviated PE will be conducted
- Collect 12-lead ECG in triplicate after supine rest of 10 minutes or per CRU standard operating procedure
- Assess supine BP/heart rate and body temperature approximately 168 hours after dosing on Day 1
- Assessment of eGFR using CKD-EPI
- Collect blood samples for PK analysis of apraglutide at 168 hours after dosing on Day 1
- Collect blood and urine samples for safety laboratory tests (hematology, clinical chemistry, and urinalysis)
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "Have you noticed any changes to your physical condition?"

- The Investigator or designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the contraception guidelines and will confirm highly effective, proper contraception is being used up to 1 month after EOT
- Review concomitant treatments
- Subjects will be instructed on all pertinent lifestyle requirements and restrictions
- Injection site assessment at approximately 168 hours post-dose
- Discharge from CRU confinement

If a subject has any clinically significant trial-related abnormalities at the conclusion of a scheduled inpatient portion of the trial, the Safety Medical Monitor (or designated representative from the Sponsor) should be notified and the subject may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the CRU and/or when outpatient follow-up is deemed appropriate, the Safety Medical Monitor (or designated representative) should be notified and the Investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

7.3.10 Day 11 (Outpatient Visit)

- Collect 12-lead ECG in triplicate after supine rest of 10 minutes or per CRU standard operating procedure
- Assess supine BP/heart rate and body temperature
- Collect blood samples for PK analysis of apraglutide at 240 hours after dosing on Day 1 during an outpatient visit
- Collect blood and urine samples for safety laboratory tests (hematology, clinical chemistry, and urinalysis), including measurement of eGFR
- Review concomitant treatments
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “Have you noticed any changes to your physical condition?”

7.3.11 Follow-up Visit Day 14±2 days (also Early Termination Visit Procedures)

Subjects will return to the CRU for a follow-up visit where the following procedures will be done. Additional follow-up visits (unscheduled) may be required to follow up on outstanding clinical events or AE(s).

- Conduct abbreviated PE and weight measurement
- The Investigator or designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the contraception guidelines and will confirm highly-effective, proper contraception is being used up to a month after EOT
- Assess supine BP/heart rate and body temperature
- Collect 12-lead ECG in triplicate after supine rest of 10 minutes or per CRU standard operating procedure
- Review concomitant treatments
- Collect blood and urine samples for safety laboratory tests (hematology, clinical chemistry, and urinalysis); a serum pregnancy test for any WOCBP

- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "Have you noticed any changes to your physical condition?"
- Injection site reaction assessment

7.4 Pharmacokinetics

Up to two blood samples of approximately 3 mL, to provide a minimum of 1.2 mL, will be collected into appropriately labeled tubes containing potassium ethylenediaminetetraacetic acid (K_2-EDTA) for measurement of plasma concentrations of apraglutide at times noted in this section (Table 7). The appropriate additives will be added to the sample collected for all PK samples if indicated. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Table 7: Pharmacokinetic Time Points

Day	Pharmacokinetic Time Points (hours)
1	0, 6, 12
2	24, 28, 36, 40
3	48, 60
4	72
5	96
6	120
7	144
8	168
11	240

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after IMP administration that are obtained within 10% of the nominal time (e.g., within 6 minutes of a 60 minute sample) relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eCRF). Collection of samples more than 10 hours after IMP administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eCRF).

Samples will be used according to objective and analysis defined in the protocol. Genetic analysis will not be performed on these plasma samples. Subject confidentiality will be maintained.

Samples collected for measurement of plasma concentration (PK) of apraglutide will be analyzed using a validated analytical method in compliance with applicable standard operating procedures.

The PK samples must be processed and shipped as indicated in the instructions provided to the Investigator/CRU to maintain sample integrity. Any deviations from the PK sample handling procedure (e.g., sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the Sponsor. On a case-by-case basis, the Sponsor can make a determination as to whether sample integrity has been compromised. No PD parameters will be evaluated in this trial.

8 Statistical Methods

The statistical evaluation of the trial will include descriptive statistics reflecting the early phase of the trial and analyses will be provided for the key endpoints.

Any deviations from the planned analyses will be described and justified in the final clinical trial report.

8.1 Determination of Sample Size

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 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 [19, 20, 21, 22].

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

In Part 1, approximately eight subjects each will be enrolled into the normal renal function group and the severe renal impairment group so that to ensure approximately six evaluable completers in each group. If Part 2 is conducted, approximately eight subjects each will be enrolled to the mild and moderate groups to ensure approximately six evaluable completers per group.

Subjects who discontinue from the trial before completing all assessments may be replaced at the discretion of the Investigator and Sponsor.

8.2 Population for Analysis

For purposes of analysis, the following populations are defined (Table 8).

Table 8: Populations Description

POPULATION	DESCRIPTION
Pharmacokinetic (PK) Concentration	The PK concentration population is defined as all subjects assigned to the IMP and treated who have at least one quantifiable concentration measured
PK Parameter	The PK parameter analysis population is defined as all subjects assigned to IMP and treated who have at least one of the PK parameters of primary interest measured
Safety	All assigned to IMP and who take at least one dose of IMP

8.3 Statistical Analysis

The Statistical Analysis Plan (SAP) will be developed and finalized prior to database lock. The SAP will describe the subject populations to be included in the analysis. Unless otherwise noted in SAP, missing values will not be imputed. An explanation will be given for any missing, unused, and spurious data affecting analysis in the relevant sections of the Clinical Trial Report (CTR). This section is a summary of the planned statistical analysis of the primary and secondary endpoints.

Part 1

Analysis of variance (ANOVA) will be used to compare the natural log transformed AUC_{inf} or AUC_{last} (if AUC_{inf} cannot be calculated) and C_{max} 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 ratio of the adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

Part 2 may be conducted if apraglutide AUC_{inf} (or AUC_{last} when AUC_{inf} cannot be calculated) GMR for severe renal impairment group compared to normal group is ≥2.0. This metric is supported by recommendations from Huang *et al* [14]. Furthermore, apraglutide was well tolerated up to 56.9 mg SC QW and very well tolerated at 28.4 mg SC QW further demonstrating the large therapeutic margin of apraglutide.

Part 2

Analysis of variance will be used to compare the natural log transformed AUC_{inf} or AUC_{last} and C_{max} 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.

Box and whisker plots for individual subject parameters (AUC_{inf} or AUC_{last} and C_{max}) will be constructed by renal function group and overlaid with geometric means.

For summary statistics and median/mean plots by sampling time, the nominal PK sampling time will be used. For individual subject plots by time, the actual PK sampling time will be used.

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.

8.4 Safety Assessments

All safety analyses will be performed on the safety population.

Adverse events, ECGs, BP, heart rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the trial to evaluate the safety of subjects. Any clinical laboratory, ECG, BP, and heart rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history, PE, and neurological examination information, as applicable, collected during the course of the trial will be considered source data. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at Screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data and will be required to be reported in the eCRF. Demographic data collected at Screening will also be reported.

Adverse event summaries will be produced by treatment group including number of participants with an event, percentage of participants with an event, and total number of events. In addition, separate tables will be produced for each category of severity.

Events categorized as SAEs and AESIs as defined by Standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) or Customer Queries (CQ) will be presented likewise.

The verbatim terms used in the eCRF by Investigators to identify AEs will be coded using the MedDRA version 23.0 or above).

The prior and concomitant medication recorded in the eCRF will be coded using the latest version of World Health Organization (WHO) Drug.

All safety continuous endpoints will be presented in summary tables.

8.5 Pharmacokinetic Analysis

8.5.1 Derivation of Pharmacokinetic Parameters Prior to Analysis

The plasma PK parameters for apraglutide following single dose administration will be derived from the concentration time profiles (Table 9). Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 9: Plasma PK Parameters

Parameter	Analyte	Definition
AUC_{last}	apraglutide	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})
AUC_{inf}	apraglutide	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time
$AUC_{0\text{-}7days}$	apraglutide	Area under the plasma concentration-time profile from time 0 to Day 7
C_{max}	apraglutide	Maximum plasma concentration
T_{max}	apraglutide	Time for C_{max}
$t_{½}$	apraglutide	Terminal elimination half-life
λ_z	apraglutide	Individual estimate of the terminal elimination rate constant
CL/F	apraglutide	Apparent clearance
Vz/F	apraglutide	Apparent volume of distribution

9 Documentation and Operational Considerations

9.1 Early Termination

Both Sponsor and the Investigator reserve the right to terminate the trial at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the subjects, appropriate regulatory authority, IRBs, etc. In terminating the trial, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

9.2 Protocol Amendments

The protocol may not be modified without written approval from the Sponsor. Protocol modifications or changes may not be initiated without prior written IRB approval, except when necessary to eliminate immediate hazards to subjects or when the changes involve only logistical or administrative aspects of the trial. Such modifications will be submitted to the IRB and written verification that the modification was submitted should be obtained.

In the event that an amendment to this protocol is required, it will be classified into one of the following categories:

- Substantial Amendments are those considered 'substantial' to the conduct of the clinical trial and are likely to have a significant impact on e.g., the safety or physical or mental integrity of the subjects, the scientific value of the trial, the conduct or management of the trial or the quality or safety of the apraglutide used in the trial, changes in the protocol assessment and the trial site team
- Non-substantial Amendments are amendments which are not considered to meet the definition of substantial

Investigators are responsible for promptly informing the IRB of any amendments to the protocol.

Documentation of IRB approval must be sent to the Sponsor immediately upon receipt.

9.3 End of Trial Report

The Sponsor will notify the competent authority of the end of the trial within a period of 90 days. The end of the trial is defined as the last subject's last visit. In case the trial is ended prematurely, the Investigator will notify the IRB and the competent authority within 15 days, including the reasons for the premature termination. The Investigator will notify the IRB immediately of a temporary halt of the trial including the reason of such an action.

Within 1 year after the end of the trial, the Sponsor will submit to the FDA a final CTR with the results of the trial including any publications/abstracts of the trial. The Principal Investigator and Sponsor's Responsible Medical Officer will be the signatories for the CTR.

9.4 Regulatory and Ethical Considerations

This trial will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki [2] and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP guidelines (latest version; [1])
- FDA guidelines along with applicable laws and regulations including the FDA GCP Code of Federal Regulations (CFR) Title 21 [3], applicable privacy laws in the country where the trial is conducted

The protocol, protocol amendments, ICF, Investigator's brochure, and other relevant documents (e.g., advertisements) must be reviewed and approved by the Sponsor and submitted to an IRB by the Investigator and reviewed and approved by the IRB before the trial is initiated.

Any amendments to the protocol will require IRB approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial subjects

The Investigator will be responsible for the following:

- Providing written summaries of the status of the trial to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB and all other applicable local regulations

9.4.1 Subject Information and Consent

All parties must ensure protection of subject personal data and must not include subject names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, the Sponsor must maintain high standards of confidentiality and protection of subject personal data.

The ICF must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The ICF used in this trial, and any changes made during the course of the trial, must be prospectively approved by the Sponsor first, thereafter the IRB before use.

The Investigator must ensure that each trial subject is fully informed about the nature and objectives of the trial and possible risks associated with participation. The Investigator, or a person designated by the Investigator, must obtain written informed consent from each subject before any trial-specific activity is performed. The Investigator must retain the original of each subject's signed consent. The subject will be provided ample time to read and ask questions on the provided ICF. The subject will be provided a copy of the signed and dated ICF.

9.4.2 Institutional Review Board

It is the responsibility of the Investigator to have prospective approval of the trial protocol, protocol amendments, ICF, and other relevant documents (e.g., recruitment advertisements, if applicable) from the IRB. All correspondence with the IRB must be retained in the Investigator Site File.

The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the Investigator must notify the IRB and Sponsor in writing, immediately after the implementation.

9.4.3 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout the trial, a subject's source data must only be linked to Sponsor's clinical trial database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes such as sex, age, or date of birth, may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its Monitor or designee's Monitor representatives from any regulatory authority (e.g., FDA), Sponsor's designated Auditors, and the appropriate IRB to review the subject's original source data and documents.

Copies of any subject source documents that are provided to the sponsor must have certain identifiable information removed (i.e., subject name, address, and other identifier fields not collected in subject eCRF).

9.4.4 Liability and Insurance

The Sponsor will cover this trial by means of an adequate insurance of the participating subjects which will be in place prior to the start of the trial.

As per local regulations, details about the insurance are described in the subject information sheet and ICF. A copy of the insurance statement is filed in the Investigator Site File and the subject can request a copy.

9.5 Reporting of Safety Concerns and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable regulatory authority in any area of the world, or if the Investigator is aware of any new information that might influence the evaluation of the benefits and risks of the IMP, Sponsor immediately of any urgent safety measures taken by the Investigator to protect the trial subjects against any immediate hazard, and of any serious breaches of this protocol and/or of ICH GCP that the Investigator has become aware.

9.6 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, as requested, to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

9.7 Informed Consent Process

The Investigator or his/her representative will explain the nature of the trial to the subject and answer all questions regarding the trial.

Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 [23], local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements [24], where applicable, and the IRB or trial site.

The Investigator must ensure that each trial subject is fully informed about the nature and objectives of the trial, the sharing of data related to the trial, and possible risks associated with participation, including the risks associated with the processing of the subject's personal data.

The subject must be informed that his/her personal trial-related data will be used by the Sponsor in accordance with applicable data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the trial and the date and time the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

If applicable, subjects must be reconsented to the most current version of the ICF(s) during their participation in the trial.

A copy of the ICF(s) must be provided to the subject. Subjects who are rescreened are required to sign a new ICF.

9.8 Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures, and the General Data Protection Regulation (EU) 2016/679 [25] to ensure protection of subject data. USA-based sites and laboratories or entities providing support for this trial must, where applicable, comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) [24]. A USA-based site that is not a Covered Entity, as defined by HIPAA, must provide documentation of this fact to the CRO. The subject's confidentiality and privacy are to be strictly held in trust by the participating sites, Investigators, their staff, the Sponsor(s) and its designees involved in the trial. This confidentiality is extended to testing of biological samples and any future testing in addition to the clinical information relating to the subject. The subject's contact information will be securely stored at each clinical site for internal use during the trial.

After subjects have consented to take part in the trial, the Sponsor and/or its designee reviews their medical records and data collected during the trial. These records and data may, in addition, be reviewed by others including the following: monitors and independent auditors who validate the data on behalf of the Sponsor; third parties with whom the Sponsor may develop, register, or market the clinical trial drug; national or local regulatory authorities; the IRB(s) which gave approval for the trial to proceed. The Sponsor and/or its designees accessing the records and data will take all reasonable precautions to maintain the confidentiality of subjects' identities, in accordance with applicable laws, regulations, and guidelines. Subjects' personal data will be stored at the trial site in encrypted

electronic form and will be password-protected to ensure that only authorized trial staff has access. To protect the rights and freedoms of natural persons with regard to the processing of personal data, subjects will be assigned a single, subject-specific numerical code. Any subject records or data sets that are transferred to the Sponsor will contain the numerical code; subject names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, subject-specific code. The trial site will maintain a confidential list of subjects who participated in the trial, linking each subject's numerical code to his or her actual identity.

The results of trials – containing subjects' unique identifying number, relevant medical records, and birth year – will be recorded. Subject to adequate safeguards, they may be transferred to and used in other countries that may not afford the same level of protection that applies within the countries where this trial is conducted. The purpose of any such transfer would include but not be limited to: to support regulatory submissions, to conduct new data analyses to publish or present the trial results, or to answer questions asked by regulatory or health authorities, or for activities that otherwise connected to the trial. In case of data transfer, the Sponsor will protect the confidentiality of subjects' personal data consistent with the clinical trial agreement and applicable privacy laws. At the end of the trial, all trial data will be archived by the Sponsor or its designee and stored for a minimal period of 25 years.

9.9 Data Handling and Record Keeping

9.9.1 Data Collection

All subject data relating to the trial will be recorded using an eCRF (conforms to 21 CFR Part 11 requirements [26]) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The location of source data will be defined in the relevant source data location form prior to trial start.

The Investigator must ensure that the eCRFs are securely stored at the trial site in encrypted electronic form and are password-protected to prevent access by unauthorized third parties.

The Investigator must permit trial-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after trial completion. It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

The Sponsor or designee will provide the trial site(s) with secure access to and training on the electronic data capture application sufficient to permit site personnel to enter or correct information in the eCRFs on each subject.

An eCRF is required and must be completed for each enrolled subject. Screen failures and reasons for those will be captured in the eCRF system. The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered on the eCRFs and any other data collection forms. Source documentation supporting the eCRF

data must indicate the subject's participation in the trial and must document the dates and details of trial procedures, AEs, other observations, and subject status.

The audit trail will show the user's identification information and the date and time of any correction. The eCRFs must be signed electronically by the Investigator to attest that the data contained on the eCRFs, including any changes made to the eCRFs, are correct and to endorse the final submitted data for the subjects for whom the Investigator is responsible.

The completed eCRFs are the sole property of the Sponsor and must not be made available in any form to third parties, except for authorized representatives of the sponsor or appropriate regulatory authorities, without written permission from the sponsor.

The Sponsor will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disc or other electronic media will be provided to the site for placement in the Investigator's trial file.

9.9.2 Database Management and Quality Control

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The Sponsor or designee is responsible for the data management of this trial, including quality checking of the data.

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the Investigator for 25 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The Investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When subject data are to be deleted, the Investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The Investigator(s) will notify the Sponsor or its designees immediately of any regulatory inspection notification in relation to the trial. Furthermore, the Investigator will cooperate with the Sponsor or its designees to prepare the Investigator site for the inspection and will allow the Sponsor or its designees, whenever feasible, to be present during the inspection. The Investigator site and Investigator will promptly resolve any discrepancies that are identified between the trial data and the subject's medical records. The Investigator will promptly provide copies of the inspection findings to the Sponsor or its

designee. Before response submission to the regulatory authorities, the Investigator will provide the Sponsor or its designees with an opportunity to review and comment on responses to any such findings.

During trial conduct, the Sponsor or its designees will conduct periodic monitoring visits to ensure that the protocol and ICH GCPs are being followed. The Monitors will review source documents to confirm that the data recorded on eCRFs are accurate. The Investigator and institution will allow the Sponsor's Monitors or designees and appropriate regulatory authorities direct access to source documents to perform this verification.

The trial site may be subject to review by the IRB, and/or to quality assurance audits performed by the Sponsor or companies working with or on behalf of the Sponsor, and/or to inspection by appropriate regulatory authorities.

It is important that the Investigator and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

9.9.3 Record Retention

To enable evaluations and/or audits from regulatory authorities or Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs, source documents), all original signed ICFs, eCRFs, SAE forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records must be retained by the Investigator according to the ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer.

If the Investigator becomes unable, for any reason, to continue to retain trial records for the required period (e.g., retirement, relocation), the Sponsor must be prospectively notified. The trial records must be transferred to a designee acceptable to the sponsor, such as another Investigator, another institution, or to the sponsor. The Investigator must obtain the Sponsor's written permission before disposing of any records, even if retention requirements have been met.

9.10 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

9.11 Trial and Site Closure

The Sponsor designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The Investigator may initiate trial-site closure at any time upon notification to the contract research organization if requested to do so by the responsible IRB or if such termination is required to protect the health of trial subjects.

Reasons for the early closure of a trial site by the Sponsor may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further trial intervention development

Trial termination information is also provided in the clinical trial agreement. If there is any conflict between the clinical trial agreement and this protocol, the clinical trial agreement will control as to termination rights.

9.12 Publication Policy and Public Disclosure

The Institution and the Investigator agree that the Sponsor shall have the sole and exclusive right to the first publication of the results of the trial.

The results of this trial may be published or presented at scientific meetings by the investigator after publication of the overall trial results or 1 year after end of the trial (or trial termination), whichever comes first.

The Investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the Sponsor 30 days before submission. This allows the Sponsor to protect proprietary information and to provide comments and the Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any trial or Sponsor intervention-related information necessary for the appropriate scientific presentation or understanding of the trial results.

For all publications relating to the trial, the Investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

Authorship of publications for the overall trial results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If there are any discrepancies between the protocol and the clinical trial agreement regarding clinical trial-related publications, the provisions of the clinical trial agreement will prevail.

9.13 Protocol Compliance and Deviations

The Investigator must conduct the trial in compliance with the protocol provided by the Sponsor and given approval/favorable opinion by the IRB and the appropriate regulatory authorities. Modifications to the protocol must not be made without agreement between both the Investigator and the Sponsor. Changes to the protocol will require written IRB and the appropriate regulatory authority approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB may provide, if applicable, regulatory authority permit, expedited review, and approval/favorable opinion for minor change(s) in ongoing trials that

have the approval/favorable opinion of the IRB. The Sponsor must ensure that all protocol modifications are submitted to the regulatory authority in accordance with the governing regulations.

If other unexpected circumstances arise that require deviation from protocol-specified procedures, the Investigator must consult with the sponsor (and IRB, as required) to determine the appropriate course of action.

The site must document all protocol deviations in the subject's source documents. In the event of a deviation expected to influence the subject safety or the estimation of the PK parameters, the site must notify the sponsor (and IRB, as required).

- Protocol deviations will be identified based on conditions related to the categories below:
- Protocol entry criteria
- Forbidden concomitant medications
- Missing evaluations for relevant endpoints
- Medications errors
- Other protocol deviations occurring during clinical trial conduct

All protocol deviations will be identified and listed where appropriate.

10 Safety

10.1 Safety Data Reporting and Collection Period

After signing informed consent, all AEs including SAEs and AESIs regardless of relationship to apraglutide will be collected, fully investigated and documented in source documents and eCRFs and will be reported either until the last protocol-specific procedure or safety follow-up.

Investigators should report any SAEs, or other AEs of concern that are believed to be related to apraglutide for up to 2 weeks following the safety follow-up visit (EOT).

Adverse events that occur between subject's ICF signature and dosing will be captured as pre-treatment AEs.

The Investigator must monitor the condition of the subject throughout the trial from the time of obtaining informed consent until the last protocol-specific procedure, whether it is the EOT visit or ET visit, or a safety follow-up period.

If an Investigator becomes aware of an SAE which occurred up to 2 weeks following the safety follow-up visit (EOT) (this includes withdrawn subjects) and he/she assesses the SAE to have a reasonable possible causality to the IMP, the case will have to be reported to the Sponsor via the Contract Research Organization (CRO) (Section 10.3.3).

The emergency contact details for the Sponsor can be found in the Investigator Site File (ISF).

10.2 Definition and Assessment of (Serious) Adverse Events and Other Safety Related Events

An AE is any untoward medical occurrence in a subject or a clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not related to the IMP [1]. Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as baseline medical conditions (medical history) and are not to be considered AEs.

The sources of AEs include:

- The subject's response to questions about his/her health (a standard nonleading question such as "How have you been feeling since your last visit?" is asked at each visit)
- Symptoms spontaneously reported by the subject
- Investigations and examinations with findings that are assessed by the Investigator to be clinically significant
- Other information relating to the subject's health becoming known to the Investigator

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

Specific information related to liver safety can be found in Section 10.10.

An SAE is classified as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to apraglutide (also applies if father was exposed to apraglutide)
- Is a medically significant event in the Investigator's judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above) [27]

Events that Do Not Meet the Definition of an SAE:

- Elective hospitalizations to administer, or to simplify trial treatment or trial procedures are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs
- Hospitalization or prolongation of hospitalization as part of a routine procedure
- Hospitalization for a survey visit, annual physicals or social reasons
- Hospitalization that does not include an overnight stay
- Elective hospitalizations for pre-existing conditions documented in the medical history that have not worsened
- Hospitalization to facilitate treatment of disease/illness with other treatment options, although these treatments are not permitted as per the protocol and will be documented as a protocol deviation

In case of doubt, an event should be reported within timelines.

Definition of Adverse Events of Special Interest

An AESI, serious or non-serious, is an AE of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring, additional information, and rapid communication by the Investigator to the Sponsor can be appropriate. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., regulators) might also be warranted in line with Council for International Organizations of Medical Sciences standards and local regulations.

The following are considered AESIs for this trial:

- Injection site reactions (ISR)
- Gallbladder, biliary, and pancreatic disease
- Fluid overload
- Hypotension
- Persistent abdominal pain

Injection site reactions

Subjects will be monitored for ISRs for at least 1 hour after IMP administration given at site, until the reaction stops. The individual symptoms of the ISR (e.g., injection site pain, injection site pruritus

[itching], injection site erythema [redness], injection site edema [swelling], injection site bruising) should be reported as AEs.

Data on local tolerability will be collected as an AESI. The following characteristics of ISRs will be documented:

- Pain
- Erythema
- Induration
- Pruritus
- Bruising

Severity and duration of these features of the ISR will be collected by the site by direct observation when IMP is administered on site. When IMP is administered at home, ISRs should be reported to the site for documentation in the subject's source documents and entry into the eCRF.

Gallbladder, Biliary and Pancreatic Disease

These should be monitored by symptoms, liver enzymes (ALT, AST, alkaline phosphatase), bilirubin, lipase, and amylase and subjects should be treated according to the Investigator's judgement.

Fluid Overload, Hypotension and Persistent Abdominal Pain

Subjects will be monitored closely for signs and symptoms related to fluid overload (e.g., edema, due to increased absorption), hypotension and persistent abdominal pain. The Investigator will document any cases and manage as per clinical practice for the subject accordingly.

10.3 Safety Reporting

10.3.1 Reporting of Adverse Events

All AEs must be reported to the CRO through the eCRF and within the data entry timeline defined for this trial and stipulated in the clinical trial agreement.

10.3.2 Reporting of Adverse Events of Special Interest

All AESIs must be reported to the CRO through the eCRF and within two weeks following the event.

10.3.3 Reporting of Serious Adverse Events

All SAEs must be reported immediately and within a maximum of 24 hours to the CRO and thereafter the CRO will report to the Sponsor of the trial.

Serious adverse event primary information should be collected through the eCRF and the reporting is done via paper form, which can be submitted via email or fax to PRA Safety.

The contact information is:

- North/South America
- Fax: [redacted]
- Email: [redacted]

The Sponsor/CRO will re-evaluate the SAE and return the form to the site, requesting clarification or follow-up information if needed. After the initial SAE report, the Investigator is required, proactively, to provide further information regarding the subject's condition.

Serious AEs resulting in death will be reported to the IRB within 7 days.

The minimum data required for a report is:

- Subject identifier (ID)
- Trial ID
- Date of enrolment
- Date and time of start of SAE
- Description of SAE
- Severity of SAE
- Assessment of causality relationship to IMP
- Name and contact details of person reporting the event

10.3.4 Reporting of Suspected Unexpected Serious Adverse Events

A suspected unexpected serious adverse event (SUSAR) for an event that is life-threatening or fatal needs to be reported to the IRB (local event via local Investigator) and competent authorities (CAs) within 7 calendar days.

All other SUSARs need to be reported to the IRB (local event via local Investigator) and CAs within 15 calendar days.

As necessary, the Sponsor must inform the Investigator, the IRB, and competent authorities participating in the clinical trial of the occurrence of a SUSAR.

For SAEs, the active reporting period begins from the time that the subject provides informed consent through the end of the trial. Serious AEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the Investigator becomes aware of them; at minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to the IMP are to be reports to the Sponsor.

10.4 Pregnancy Reporting

Pregnancies occurring in this trial and within 90 days after dose are collected and reported. Unless described otherwise, pregnancies with or without serious outcomes are reportable within 24 hours of awareness to the CRO.

Although pregnancies themselves are not considered to be (S)AEs, the Investigator must report any pregnancies reported during the trial to the CRO within the timelines for SAE reporting. The trial subject will give consent on enrolment that the investigator will report any pregnancy occurring after consenting to 90 days after the dosing and that the subject will be asked to provide information about the pregnancy, delivery and the health of the infant until the age of 1 month. The Investigator must report information on pregnancies and follow-up within 14 calendar days of obtaining the information. Pregnancy complications must be recorded as (S)AEs, as appropriate. If the infant has a congenital anomaly/birth defect this must be reported and followed up as a SAE.

10.5 Medication Errors

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the IMP
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject

Whether or not the medication error is accompanied by an AE, as determined by the Investigator, the medication error is captured on the medication error version of the AE page, and if applicable, any associated AE(s) are capture on the AE eCRF.

10.6 Severity Assessment

The Investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these are defined as follows:

- MILD: Does not interfere with subject's usual function
- MODERATE: Interferes to some extent with subject's usual function
- SEVERE: Interferes significantly with subject's usual function

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE.

The NCI-CTCAE system [17] will be used to grade the severity of the SAEs, AEs and AESIs.

10.7 Causality Assessment

Both the Investigator and Sponsor will assess the causality of the event in relation to the IMP, based on the criteria listed in the ICH E2A guidelines [27]:

The Investigator must also systematically assess the causal relationship of AEs to IMP(s)/trial treatment (including any other non-IMPs, radiation therapy, etc.) using the definitions described below. Decisive factors for the assessment of causal relationship of an AE to the IMP include, but may not be limited to, temporal relationship between the AE and the IMP, known side effects of IMP, medical history, concomitant medication, course of the underlying disease, trial procedures.

Not related: Not reasonably related to the IMP. Adverse event could not medically (pharmacologically/clinically) be attributed to the trial IMP in this clinical trial protocol. A reasonable alternative explanation must be available. Adverse events reported as “unlikely” related and “unrelated” will be considered unrelated for reporting purposes.

Related: Reasonably related to the IMP. Adverse event could medically (pharmacologically/ clinically) be attributed to the IMP under trial in this clinical trial protocol. Table 10 can be used to differentiate between the AEs related to the IMP. Adverse events reported as definitely, probably and possibly related will be considered as “related” for reporting purposes.

Table 10: Assessment of Causality of Adverse Events

	Assessment of Causality				
	Definitely	**Probably**	**Possibly**	**Unlikely**	**Not Related**
Clearly due to extraneous causes	N	N	N	N	Y
Reasonable temporal association with drug administration	Y	Y	Y/N	N	N
May be produced by subject clinical state, etc.	N	N	Y	Y	Y
Known response pattern to IMP	Y/N	Y/N	N	N	N
Disappears or decreases on cessation or reduction in dose	Y	Y/N	N	N	N
Reappears on re-challenge (if possible)	Y	N	N	N	N

IMP=investigational medicinal product; Y=yes; N=no.

10.8 Adverse Event Outcome

An AE must be followed until recovery whether the trial has ended or not. The outcome must be classified according to the categories shown below:

- **Recovered/Resolved:** Resolution of an AE with no residual signs or symptoms
- **Recovered/Resolved with Sequelae:** Resolution of an AE with residual signs or symptoms
- **Recovering/Resolving:** Improvement of an AE
- **Not Recovered/Not Resolved (Continuing):** Either incomplete improvement or no improvement of an AE such that it remains ongoing
- **Fatal:** The outcome of an AE is death. “Fatal” must be used when death is at least possibly related to the AE
- **Unknown:** The outcome of an AE is not known (e.g., a subject lost to follow-up)

10.9 Treatment Given

The Investigator must ensure adequate medical care is provided to subjects for any AEs. In addition, the Investigator must describe whether any treatment was given for the AE. This information must be document on subject source.

10.10 Liver Safety: Suggested actions and Follow-up Assessments for Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience

a transaminase elevation above 3 × ULN should be monitored within 48 hours and alternate causes of hepatitis should be investigated to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (i.e., AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria; [19]) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

Discontinuation of treatment should be considered if:

- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN and (TBL >2xULN or INR >1.5)
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the Investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, creatine kinase, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time/international normalized ratio, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a co-formulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (e.g., biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such** potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

11 References

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