Crinetics Pharmaceuticals, Inc.

Protocol #: CRN00808-03

EudraCT # 2018-002230-20

NCT # 03789656

AN OPEN LABEL EXPLORATORY STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS AND EFFICACY OF CRN00808 IN PATIENTS WITH ACROMEGALY TREATED WITH SOMATOSTATIN ANALOGUE BASED TREATMENT REGIMENS (ACROBAT EDGE)

Document Type:	Clinical Study Protocol
Investigational Medicinal Product:	CRN00808 (non-peptide small molecule investigational drug) Oral SST2 Agonist
Phase of Development:	Phase 2
Indication:	Acromegaly in adult patients
Sponsor:	Crinetics Pharmaceuticals, Inc. 10222 Barnes Canyon Road, Building #2 San Diego, CA 92121 USA
Protocol Version:	3.0
Protocol Date:	07 June 2019

SPONSOR APPROVAL PAGE

Protocol #: CRN00808-03

An open label exploratory study to evaluate the safety, pharmacokinetics and efficacy of CRN00808 in patients with acromegaly treated with somatostatin analogue based treatment regimens (ACROBAT EDGE)

Protocol Version: 3.0

Protocol Date: 07 June 2019

This protocol has been reviewed and approved by Crinetics Pharmaceuticals, Inc.:

_____ _____

[redacted], MD
[redacted]

Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

Protocol #: CRN00808-03

An open label exploratory study to evaluate the safety, pharmacokinetics and efficacy of CRN00808 in patients with acromegaly treated with somatostatin analogue based treatment regimens (ACROBAT EDGE)

Protocol Version: 3.0

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I have read and I understand this protocol. I will conduct this protocol as outlined therein and will make all reasonable efforts to complete the study within the designated time.

I agree to conduct this trial in accordance with the Declaration of Helsinki, the International Council for Harmonization (ICH), Guideline for Good Clinical Practice (GCP), and all applicable regulatory requirements.

I will provide copies of the protocol and access to all information furnished by Crinetics Pharmaceuticals, Inc. to study personnel under my supervision. I will discuss material with them to ensure that they are fully informed about the study.

I understand that the study may be terminated or enrollment suspended at any time by Crinetics Pharmaceuticals, Inc., with or without cause, or by me, if it becomes necessary to do so in the best interests of the study subjects.

Site name: _____

Site address: _____

Phone number: _____

Principal Investigator:

Name and title (printed): _____

Signature: _____

Date: _____

CONTACT LIST

A separate contact information sheet will be provided to each clinical site.

Serious Adverse Event (SAE) reporting information is found in Section 6.1.2.

General advice on protocol procedures should be obtained through the monitor assigned to the study site.

Contact Type	Contact Information
Medical Monitoring	[redacted], MD CRO Senior Director, Drug Safety and Regulatory Accelsiors CRO and Consultancy Services Ltd. 66, Šarplaninska Str. 21000 Novi Sad, Serbia Cell: [redacted]
CRO Pharmacovigilance (SAE and pregnancy reporting, emergency unblinding)	Accelsiors CRO and Consultancy Services Ltd. 66, Šarplaninska Str. 21000 Novi Sad, Serbia e-mail: [redacted] Telephone number: [redacted]

STUDY VENDOR LIST
(Refer to the Study Reference Manual for full contact information)

Study Responsibility	Vendor
Central IGF-1 Reader	[redacted], MD Medizinische Klinik und Poliklinik IV, Klinikum der Universitaet Muenchen, 80336 Munich, Germany
Central Laboratory (All safety and bioanalytical labs will be shipped to [redacted])	[redacted]
Bioanalytical Laboratory (CRN00808 PK)	[redacted]
Bioanalytical Laboratory (UGT1A1 genotype Sample)	[redacted]
Cardiac Monitoring	[redacted]
Bioanalytical Laboratory (lanreotide and octreotide PK)	[redacted]

Study Responsibility	Vendor
Drug Product Packaging and Distribution	[redacted]
Subject Travel and Reimbursement Support (Optional Service)	[redacted]
Mobile Research (Optional Service)	[redacted]

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Crinetics Pharmaceuticals, Inc.
Title of Study: An open label exploratory study to evaluate the safety, pharmacokinetics and efficacy of CRN00808 in patients with acromegaly treated with somatostatin analogue based treatment regimens (ACROBAT EDGE)
Study Code: CRN00808-03
Phase of Development: Phase 2
Name of Investigational Product: CRN00808 (non-peptide small molecule investigational drug) - Oral SST2 Agonist
Name of Active Ingredient: [redacted] ([redacted])
Study Centers: Approximately 50 centers in the United States, Europe, South America, and Oceania.
Study Objectives: • To evaluate the efficacy of CRN00808 in acromegaly subjects treated with somatostatin analogue based treatment regimens; • To evaluate the safety and tolerability of CRN00808 in acromegaly subjects; • To evaluate the pharmacokinetics (PK) of CRN00808 in acromegaly subjects.
Study Duration: The expected duration of study participation for each subject is up to 23 weeks, including up to 6 weeks of Screening, up to 13 weeks of Treatment Period and up to 4 weeks of Follow-up Period.
Study Design and Methodology: This is an open label dose blinded exploratory study designed to evaluate the safety, PK and efficacy of CRN00808 in subjects with acromegaly that are treated with somatostatin analogue (SSA) based treatment regimens. The study will consist of the following periods: • Screening Period (4-6 weeks); • Treatment Period (up to 13 weeks); • Follow-up Period (up to 4 weeks). Approximately 45 subjects on stable doses of SSA based pharmacotherapy for the treatment of acromegaly will be recruited for this clinical trial.

SCREENING PERIOD

The purpose of the 4-6-week Screening Period is to perform all investigations required to establish a subject's eligibility for the study. Once all assessments are completed and eligibility of the subjects are verified by the Investigator and confirmed by Medical Monitor (MM), the subject will be enrolled in the Treatment Period of the study.

Informed and written consent will be obtained from the subjects at V1a prior to any study specific procedure. Eligibility for enrollment into the Treatment Period of the study will be in part determined by two IGF-1 values measured during the Screening Period. The first measurement will occur at V1b (0-2 weeks after V1a) and will be drawn immediately prior to the subject's regularly scheduled dose of octreotide LAR, lanreotide depot or pasireotide LAR. The second IGF-1 measurement will be performed at V2 which will occur 1-2 weeks after V1b. In order to be eligible to enter the Treatment Period, the Screening IGF-1 measurements (performed by the study central laboratory) must fall into the ranges specified for one of the following groups:

- **Group 1:** Partial responders on a stable treatment of octreotide LAR or lanreotide depot (at least one Screening IGF-1 value must be >ULN, and the V2 value must be ≤2.5×ULN);
- **Group 2:** Partial responders on a stable combination treatment of SSA (i.e., octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (at least one Screening IGF-1 value must be >ULN, and the V2 value must be ≤2.5×ULN);
- **Group 3:** Complete responders on a stable combination treatment of SSA (i.e., octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (mean of Screening IGF-1 values must be ≤ULN);
- **Group 4:** Complete responders on a stable dose of pasireotide LAR (mean of Screening IGF-1 values must be ≤ULN);
- **Group 5:** Complete responders on a stable combination treatment of SSA (i.e., octreotide LAR or lanreotide depot) and pegvisomant (mean of Screening IGF-1 values must be ≤ULN).

All other assessments performed during the Screening Period are detailed in Table 1.

TREATMENT PERIOD

During the 13-week Treatment Period, subjects will attend 12 study visits which include study drug dispensing, blood sample collection, safety assessments, and other study procedures as indicated in Table 1. The Treatment Period starts with the first dose of study drug ([redacted] for all subjects) at V3, which occurs approximately 4 weeks after V1b. Subjects enrolling into the Treatment Period will not continue their standard acromegaly treatment until study completion or early termination. While in the Treatment Period, the subjects will self-administer the study drug at approximately the same time in the morning, once daily after an overnight fast of at least 6 hours. Fasting will continue for at least two hours post-dose. At visits V3/W1, V6/W4, V9/W7, V12/W10, and V14/W13 the study drug is to be administered at the study center, also

under fasting conditions. During the entire Treatment Period, the subjects are expected to swallow four capsules (Size 2) with water every day.

During the V6/W4 and V9/W7, the dose may be titrated up in a blinded fashion, provided the preceding IGF-1 values collected in V4/W2, and in V7/W5, respectively, are >0.9×ULN and the current dose is tolerated by the subject. At V12/W10, the dose may be titrated up in a blinded fashion, provided the preceding IGF-1 value collected in V10/W8 is >ULN and the current dose is tolerated by the subject.

The investigator will assess whether the subject is tolerating the current dose and is blinded to IGF-1 results. The central IGF-1 reader will have access to the unblinded IGF-1 data and will determine if the IGF-1 results meet criteria for potential increase in study drug dose. The Investigator will confirm the subject is eligible for an increase in the study drug dose based on tolerability at V5/W3, V6/W4, V8/W6, V9/W7, V11/W9 and V12/W10. If tolerability is confirmed and the IGF-1 reader has determined that IGF-1 has not met adequate suppression criteria at the previous visit, a blinded blister card containing the appropriate higher dose will be assigned at the V6/W4, V9/W7 and/or V12/W10. Dose increases in [redacted] increments will be allowed only at the V6/W4 (from [redacted]) V9/W7 (from [redacted]) and V12/W10 (from [redacted]). No further up-titrations will be allowed. The daily dose will not exceed [redacted].

If IGF-1 suppression as defined above has been achieved with a tolerated dose, the dose will not be changed. At any time during study drug dosing, including at V6/W4, V9/W7 and V12/W10, study drug dosing may be reduced in a blinded fashion on one occasion if the investigator determines that the subject is not adequately tolerating the study drug. In general, a suspected CRN00808-related AE sufficient to result in a study drug dose reduction would be expected to be of Grade 3 (Severe) intensity.

An unblinded CRO designate will oversee the correct assignment of new blinded dose blister cards taking into account information from the investigator and from the central IGF-1 reader.

Subjects will return to the study center at the end of W13 (i.e., V14) on the last day of dosing. No further treatment with the study drug will be allowed after completion of V14/W13.

FOLLOW-UP PERIOD

During this 4-week-period subjects will attend 2 study visits (V15/W15 and V16/W17) and are expected to be off any acromegaly treatment, including CRN00808. All other assessments during the Follow-up Period are described in Table 1. Criteria for resumption of standard acromegaly treatment are provided in detail in Section 3.1.

Number of Subjects (planned): Approximately 45 male and female subjects with a confirmed acromegaly diagnosis who fall into one of the five groups as described above.

Groups 1 and 2 will contribute at least 30 of the approximately 45 subjects enrolled.

Diagnosis and Main Criteria for Inclusion:

Approximately 45 adult subjects will be considered for enrollment in the study if they meet all the inclusion and none of the exclusion criteria.

Inclusion criteria:

1. Medically stable male and female subjects 18 to 75 years of age, inclusive, with a confirmed acromegaly diagnosis, who meet the protocol defined criteria (see Section 3.2) for a partial or complete responder to somatostatin analogue based therapy. A stable dose is defined as no changes in acromegaly medication doses in the last 3 months;
2. Diagnosis of active acromegaly confirmed by the Investigator and approved by the Medical Monitor. At a minimum, there must be documentation available of a pituitary tumor and elevated IGF-1 in the past. In subjects who have undergone pituitary surgery, elevated IGF-1 measured three or more months after surgery must be documented. A head MRI (or CT Scan for subjects unable to undergo MRI) with pituitary imaging will be performed during the Screening Period unless recent documented scan performed within 6 months prior to Screening is available;
3. Subjects with hypothyroidism must be on stable treatment for at least 3 months with normal free T4 levels and should be clinically euthyroid at Screening as determined by the investigator;
4. Subjects with adrenal insufficiency must be on adequate adrenal replacement therapy at the time of Screening as determined by the investigator;
5. If the subject is female, she must be of non-childbearing potential (defined as either surgically sterilized [i.e., hysterectomy, bilateral salpingectomy, or bilateral oophorectomy] or at least 1 year of amenorrhea) OR must agree to use highly effective or two clinically acceptable methods of contraception from the beginning of Screening to the last study visit.
    - Acceptable highly effective methods of contraception include intrauterine device (IUD); intrauterine system (IUS); bilateral tubal occlusion (must be documented); non-oral hormonal contraceptives; desogestrel-based progestin-only oral contraceptives; vasectomized partner (must be documented); or sexual abstinence (only when it is the usual and preferred lifestyle of the subject). Clinically acceptable methods of birth control include male or female condom with or without spermicide; norethindrone-based progestin-only oral contraceptives; or cap, diaphragm, or sponge with spermicide. Note that simultaneous use of male and female condoms with or without any other contraception methods is not permitted. Oral hormonal contraceptives containing estrogens are not permitted.

6. If the subject is male, the subject must use a condom, or his female partner of childbearing potential must use an effective form of contraception as described above, from the beginning of Screening to the last study visit. Male subjects must also agree not to donate sperm for the duration of the study and until at least 3 months after the last dose of the study drug;
7. Subjects must be willing and able to comply with the study procedures as specified in the protocol and comply with the study treatment;
8. Negative results on a test for the following drugs during Screening: amphetamine, barbiturates, cocaine, methamphetamine, methadone, opiates, phencyclidine, and methylenedioxymethamphetamine;
9. Written Informed Consent provided prior to any study related procedures.

Exclusion criteria:

1. Treatment naïve acromegaly subjects;
2. Acromegaly subjects who had pituitary surgery within 6 months prior to Screening or subjects in Group 3, 4, or 5 who have undergone pituitary radiation therapy at any time prior to the study entry. A history of radiation therapy is not a restriction for subjects in Group 1 or 2. If a subject in Group 3, 4, or 5 has undergone pituitary radiation therapy ≥4 years prior to Screening and has had a documented IGF-1 ≥1.3×ULN within 2 years prior to Screening OR if a subject has undergone pituitary radiation therapy between 3 and 4 years prior to Screening and has had a documented IGF-1 ≥1.3×ULN within 1 year prior to Screening, the subject may be included in the study;
3. Subjects with any clinically significant concomitant disease including but not limited to cardiovascular disease; moderate or severe renal insufficiency (eGFR<60 mL/min/1.73 m^2); or significant liver disease (including cirrhosis);
4. History or evidence of any of the following within the previous 6 months: myocardial infarction, cardiac surgery revascularization (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty), cerebrovascular accident or stroke or transient ischemic attack (TIA). Syncope or marked presyncope that is unexplained or related to cardiovascular disease within the last 5 years;
5. Any of the following conditions: personal history of cardiac arrest or long QT syndrome, evidence for a familial sudden death syndrome, hemodynamically significant cardiac valvulopathy, greater than Canadian Cardiovascular Society Class 1 angina pectoris or unstable angina, greater than NYHA Class 1 congestive heart failure, ongoing episodes of symptomatic bradycardia (i.e., bradycardia associated with significant dizziness, lightheadedness, or loss of consciousness), known history of sustained ventricular tachycardia, hemodynamically significant pulmonary arterial hypertension; uncontrolled symptomatic supraventricular tachycardia, uncontrolled atrial fibrillation (chronic

persistent atrial fibrillation that is appropriately rate controlled and anticoagulated is acceptable for inclusion), type 2 second degree or third degree atrioventricular block;

6. Based on Holter monitor performed during the Screening Period: symptomatic bradycardia (i.e., bradycardia associated with significant dizziness, lightheadedness, or loss of consciousness), type 2 second degree or third degree atrioventricular block, pause >3 sec, sustained ventricular or supraventricular tachycardia, previously undiagnosed paroxysmal atrial fibrillation, or torsades de pointes;
7. Supine systolic blood pressure >150 mmHg and/or supine diastolic blood pressure >95 mmHg at Screening (if the initial measurement is out of range, may be repeated 2 more times after 15 min and exclusion will be based on the average of the three measurements);
8. Resting (at least 10 minutes) palpated pulse rate <50 bpm or >105 bpm at Screening. If either of these criteria are met, the assessment should be repeated 2 more times and the average should be used to determine the subject's eligibility;
9. QTcF interval >450 msec (or QTc >480 msec in the presence of a bundle branch block) or PR interval >240 msec at Screening based on a central reading of an average of 3 ECGs each separated in time by approximately 1 minute after the subject has rested supine for at least 10 minutes;
10. Currently receiving medications that are known to be associated with torsades de pointes listed in Appendix 2 - Medications Associated with Torsades De Pointes;
11. Currently receiving medications that are known to cause heart rate slowing (beta-blockers, verapamil, diltiazem, or ivabradine) if resting heart rate at Screening is <60 bpm;
12. Currently receiving medications that are strong inducers or inhibitors of CYP3A4 (see Protocol Section 4.7.2);
13. Subjects with autonomic disease (caused by diabetes or Parkinson's disease);
14. Subjects with symptomatic cholelithiasis;
15. Subjects with amylase and/or lipase levels >2×ULN, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2×ULN, total bilirubin >1.5×ULN, and/or creatinine >1.5×ULN at Screening. Subjects with previously diagnosed Gilbert's syndrome not accompanied by other hepatobiliary disorders and associated with total bilirubin <3 mg/dL (<51.3 µmol/L) and direct bilirubin ≤ULN will be permitted;
16. Subjects who are complete responders (both Screening IGF-1 values ≤ULN) to octreotide LAR or lanreotide depot monotherapy;
17. Subjects taking octreotide LAR at a dose higher than 40 mg, or lanreotide depot at a dose higher than 120 mg, or pasireotide LAR higher than 60 mg;
18. Subjects who usually take octreotide LAR, lanreotide depot or pasireotide LAR less frequently than every 4 weeks (e.g., every 6 weeks or 8 weeks);

19. Subjects who have undergone major surgery/surgical therapy for any cause within 4 weeks prior to Screening;
20. Subjects with poorly controlled diabetes mellitus defined as having a $HbA1_c$ ≥8.5% (69 mmol/mol);
21. Subjects with diabetes treated with insulin for less than 6 weeks prior to the study entry, or with an unstable insulin dose in 6 weeks prior to the study entry;
22. Subjects with clinically significant abnormal findings during the Screening Period, and any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardize the subject's safety or ability to complete the study;
23. Female subjects who are pregnant or lactating. Absence of pregnancy will be confirmed by serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative urine hCG pregnancy test at V3 prior to drug administration;
24. Subjects with hepatitis B, Human Immunodeficiency Virus (HIV), or hepatitis C infection. Subjects with previous hepatitis C infection that is now cured may be eligible;
25. Subjects with known history of, or current alcohol or drug abuse, within the last 12 months;
26. Subjects with any mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study, and/or evidence of poor compliance with medical instructions;
27. Subjects with a known allergy or hypersensitivity to any of the test materials or related compounds;
28. Subjects who have been treated with proton pump inhibitors and/or H2 blockers within 2 weeks prior to Screening;
29. Subjects with active malignant disease within the last 5 years with exception of basal and squamous cell carcinoma of the skin with complete local excision and resected carcinoma in situ of cervix;
30. An employee or immediate family member of an employee of Crinetics;
31. Participation in any previous trial with CRN00808, except for subjects who have screen failed study CRN00808-02;
32. Subjects who have been dosed with an investigational drug (either approved or not approved) in any prior clinical study within 30 days or 5 half-lives (whichever is longer) prior to Screening.

Investigational Product, Dosage and Mode of Administration (CRN00808)

Active substance: [redacted]

Indication: acromegaly in adult subjects

Strength: [redacted] or [redacted] (based on freebase CRN00808)

Dosage form: capsules

During the Treatment Period, subjects will receive an oral once daily dose of either [redacted] based on the titration schedule.

Subjects should avoid exposure of skin or eyes to direct sunlight or UV light for the duration of the study and for at least 10 days after receiving the last dose of study drug.

Reference Product Dosage and Mode of Administration

Not applicable.

Dose selection: The dose range of CRN00808 was selected based on PK and PD data collected in healthy volunteers, and a comparison of octreotide and lanreotide PK and PD data in healthy volunteers with efficacy data in acromegaly patients.

In the previous study in healthy volunteers, single doses up to [redacted] and daily administration of up to [redacted] CRN00808 for up to 10 days identified [redacted] as the lowest dose that achieved maximal suppression of IGF-1 in healthy volunteers. Therefore, [redacted] CRN00808 was selected as the starting dose in acromegaly subjects.

It is expected that partial responders to current pharmacotherapies used for the treatment of acromegaly will require a higher dose. Therefore, titration is allowed up to a dose of [redacted] CRN00808 in subjects whose IGF-1 is not normalized by lower doses.

Dosing holidays and discontinuation of dosing: When in the Investigator's judgment the study drug is not tolerated, the study drug may be held for up to 7 days on one occasion during the study followed by resumption of the study drug at a reduced dose.

Subjects can be discontinued from study treatment or the study as defined in Section 3.2.3.

Study Endpoints

EFFICACY ENDPOINTS:

Primary endpoint:

The primary endpoint is the change from baseline (mean of Screening values) in IGF-1 level at W13.

Key Secondary endpoints:

- Proportion of subjects with the mean of their last two consecutive IGF-1 measurements ≤ULN;
- Proportion of subjects with the mean of their last two consecutive IGF-1 measurements ≤1.5×ULN;

Exploratory endpoints:

- Proportion of subjects who achieve serum GH <5.0 ng/mL at W13.
- Proportion of subjects who achieve serum GH <2.5 ng/mL at W13;
- Change from baseline in serum GH levels measured at W13;
- Change from baseline in serum [redacted] levels measured at W13;
- Increase in serum GH, IGF-1, and [redacted] levels 3+ weeks after withdrawal of CRN00808;
- Change from baseline in symptoms of acromegaly as measured by total [redacted] score at W13;
- Change from baseline in symptoms of acromegaly as measured by individual [redacted] score at W13;
- Change from baseline in [redacted] score at W13;
- Change from baseline in [redacted] at W13;
- Change from baseline in investigator assessed symptoms of acromegaly at W13;
- Change from baseline in PGI-S scores at W13;
- PGI-I scores at W13;
- Plasma concentrations of CRN00808.

SAFETY ENDPOINTS:

- Adverse events (AEs)/Treatment-emergent Adverse Events (TEAEs) throughout the study;
- Clinical laboratory tests (hematology, serum chemistry and urinalysis) at each post-baseline study visit;
- Vital signs at each post-baseline study visit;
- Physical examinations at each post-baseline study visit;
- 12-lead ECG at each post-baseline study visit;
- fT3, fT4, anti-thyroid antibody, TSH, cortisol, ACTH, LH, FSH and prolactin at each post-baseline study visit;
- Gall bladder ultrasound.

STATISTICAL CONSIDERATIONS

Sample Size Calculation

Approximately 45 subjects are planned to be enrolled in the study. At least 30 subjects from Groups 1 and 2 will be enrolled, i.e., a cap of N=15 is set for the sum of the number of subjects in Group 3 to 5.

The primary objective of this study is to evaluate efficacy (IGF-1 levels) in subjects who are partial responders to somatostatin analogue based treatment regimens. As such, the sample size is chosen to provide sufficient clinical experience to evaluate IGF-1 changes descriptively and is not formally powered for hypothesis testing. Summary statistics for the primary endpoint will be provided.

Analysis Datasets

Safety Analysis Set comprises all subjects who received at least one dose of the study medication. The Safety Analysis Set will be used for all safety analyses and for some of the secondary efficacy endpoints.

Efficacy Analysis Set comprises all subjects from Groups 1 and 2 who received at least one dose of the study medication. The Efficacy Analysis Set will be used for the evaluation of the primary efficacy endpoint and for some of the secondary efficacy endpoints.

Per Protocol Analysis Set (PP) comprises all subjects from the Efficacy Analysis Set having no major protocol deviation affecting treatment efficacy. The PP analysis set will be used for supportive efficacy analyses.

Efficacy Evaluation

For the primary endpoint, change from baseline (mean of Screening values) in IGF-1 level at W13, descriptive statistics (n, mean, SD, 90% CI of mean, min, max, median) will be presented on the Efficacy Analysis Set and on the PP Analysis Set.

For all other efficacy endpoints descriptive statistics will be performed on the Efficacy Analysis Set. In addition, efficacy data from Groups 3, 4 and 5 will also be summarized.

Safety Evaluation

Safety endpoints will be summarized with descriptive statistics and shift tables where applicable.

PK Evaluation

Plasma concentration will be summarized by baseline status (controlled or partially controlled) and overall using descriptive statistics.

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List of Abbreviations and Acronyms

[redacted]	[redacted]
ACTH	Adrenocorticotropic hormone
AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-24}	Area under the plasma concentration-time curve from time 0 to 24 hours
Ba	Basophils
CA	Competent Authority
cAMP	Cyclic adenosine monophosphate
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence Interval
CNS	Central nervous system
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
C_{max}	Maximum plasma concentration
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture

EMA	European Medicines Agency
Eo	Eosinophils
EU	European Union
FSH	Follicle stimulating hormone
fT3	Free triiodothyronine
fT4	Free thyroxine
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GH	Growth hormone
GHRH	Growth hormone-releasing hormone
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
h	Hour(s)
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
HEENT	Head (external), Eyes, Ears, Nose and Throat
hERG	Human-ether-a-go-go-related gene
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization

IEC	Independent Ethics Committee
IGF-1	Insulin-like growth factor-1
[redacted]	[redacted]
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive response technology system
IUD	Intrauterine device
IUS	Intrauterine system
kg	Kilogram
L	Liter
LDH	Lactate Dehydrogenase
LH	Luteinizing hormone
Lym	Lymphocytes
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
mg	Milligram
min	Minutes
MM	Medical Monitor
MNAR	Missing not at random

Mono	Monocytes
µg	Microgram
Ne	Neutrophils
NOAEL	No observed adverse effect level
ng	Nano gram
OGTT	Oral glucose tolerance test
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PLT	Platelets
PP	Per-protocol Analysis Set
QA	Quality Assurance
QC	Quality Control
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAD	Single Ascending Dose
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SOP	Standard Operating Procedure
SSA	Somatostatin Analogues
SST2	Somatostatin receptor 2
SST3	Somatostatin receptor 3
SST5	Somatostatin receptor 5

SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Events
TIA	Transient ischemic attack
TSH	Thyroid stimulating hormone
$t_{1/2}$	Terminal half-life
t_{max}	Time to maximum serum concentration
ULN	Upper limit of normal
WBC	White Blood Cell
WHO	World Health Organization
WMA	World Medical Association

1 INTRODUCTION

Acromegaly is typically caused by a growth hormone (GH) secreting tumor in the pituitary. Excess GH secretion results in excess secretion of insulin-like growth factor-1 (IGF-1) from the liver, which causes bone overgrowth, organ enlargement, and changes in glucose and lipid metabolism. The symptoms of acromegaly include abnormal growth of hands and feet and changes in shape of the bones that result in alteration of facial features. Overgrowth of bone and cartilage and thickening of tissue leads to arthritis, carpal tunnel syndrome, joint aches, enlargement of lips, nose and tongue, deepening of voice due to enlarged vocal cords, sleep apnea due to obstruction of airways, and enlargement of heart, liver, and other organs. Additional symptoms include thick, coarse, oily skin, skin tags, excessive sweating and skin odor, fatigue and weakness, headaches, impaired vision, goiter, decreased libido, menstrual abnormalities in women, and erectile dysfunction in men (Melmed and Kleinberg, 2016; Carroll and Jenkins, 2016; NIDDK diseases online health information).

The major goals of treatment are to normalize serum GH and IGF-1, relieve pressure of the growing tumors, treat hormonal deficiencies, and normalize pituitary function. Surgical removal of pituitary adenoma, if possible, is the first option and often results in rapid symptom improvement. Parenterally administered somatostatin agonists are the primary pharmacological treatment options for patients that are not candidates for surgical removal of the tumor or when surgery is only partially successful or unsuccessful in achieving treatment goals (Melmed and Kleinberg, 2016; Carroll and Jenkins, 2016; NIDDK diseases online health information). Parenteral somatostatin analogs require large bore needles for monthly injections which often need to be administered by health care providers. Additionally, because these injections are depot preparations, it is difficult to titrate or individualize treatment goals for optimal patient outcomes. These agents when used as monotherapy achieve IGF-1 normalization in approximately 50% of patients. The inability of physicians to quickly adjust doses and dosing regimens likely contributes to reduced responder rates for somatostatin analog-based pharmacotherapy.

CRN00808 is a non-peptide, orally bioavailable, somatostatin agonist that is under development for the treatment of acromegaly. Clinical data to date suggest that once daily CRN00808 administration for up to 10 days can result in IGF-1 lowering in healthy volunteers, however it has not yet been evaluated in patients with acromegaly. The purpose of this study is to evaluate the efficacy of CRN00808 in acromegaly subjects treated with somatostatin analogue based treatment regimens.

Additional details on the background of acromegaly, treatment options, and nonclinical and clinical data on CRN00808 can be found in the current Investigator's Brochure.

1.1 Rationale

An orally bioavailable nonpeptide somatostatin agonist that normalizes hormone levels in acromegaly patients should improve patient compliance and quality of life by eliminating painful injections and reduce the need for frequent physician office visits. Additionally, it potentially allows physicians to quickly determine a dosing regimen for superior outcomes compared to

existing therapies. To our knowledge, CRN00808 will be the first nonpeptide oral somatostatin agonist to enter clinical trials in patients with acromegaly.

1.1.1 Justification of Dose and Dose Regimen

In this study, subjects will switch from their current monthly depot regimen of: 1) octreotide LAR or lanreotide depot; 2) combination treatment of SSA (i.e., octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline); 3) combination treatment of SSA (i.e., octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline); 4) pasireotide LAR; or 5) combination treatment of SSA (i.e., octreotide LAR or lanreotide depot) and pegvisomant to once daily regimen of oral CRN00808 without a washout to loss of IGF-1 control. A complete washout would require 8-12 weeks after last dose due to the long half-life of the depot preparations. Such a design is not reasonable because the hormone levels would become uncontrolled (i.e., return to elevated GH and IGF-1 levels) and patients would likely experience a return of symptoms for an extended period (washout plus achieving steady state with an optimal dose of CRN00808).

The starting dose of [redacted] CRN00808 was found to be the lowest dose that was maximally effective in suppressing IGF-1 in healthy volunteers at steady state and this level of suppression mirrored that achieved by either octreotide or lanreotide. For both of these peptide drugs, the trough plasma concentrations that result in maximal IGF-1 suppression in healthy volunteers (Tiberg et al, 2015 and Kuhn et al, 1994) are similar to trough concentrations that result from approved doses at steady state (approved FDA labels for octreotide and lanreotide). Therefore, [redacted] CRN00808 is considered to be a suitable starting dose in subjects.

The rationale for the proposed titration design is also supported by the goal of maintaining and/or attempting to return subjects to a biochemically controlled state. Subjects will be switched from their depot to a [redacted] starting dose of CRN00808. Because some subjects who are partial responders at the study entry or those who were on previous combination therapy, may require higher doses of the study drug, the protocol allows for dose up-titration to doses of [redacted] in a sequential manner. The [redacted] dose will only be administered to subjects who are tolerating the [redacted] dose and do not achieve IGF-1 ≤ULN. The dose titration design allows the dose of CRN00808 to be increased (if necessary) as the plasma concentrations of octreotide, lanreotide or pasireotide taper down. It is expected that by the end of the titration period, the concentrations of octreotide, lanreotide or pasireotide will be undetectable or too low to contribute to efficacy. The protocol also allows for a study drug dose reduction in the event that a dose is not tolerated in the judgment of the investigator. This dose-titration design reflects how the drug is likely to be used in clinical practice for majority of the patients.

2 STUDY OBJECTIVES

- To evaluate the efficacy of CRN00808 in acromegaly subjects treated with somatostatin analogue based treatment regimens;
- To evaluate the safety and tolerability of CRN00808 in acromegaly subjects;
- To evaluate the pharmacokinetics (PK) of CRN00808 in acromegaly subjects.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is an open label dose blinded exploratory study designed to evaluate the safety, PK and efficacy of CRN00808 in subjects with acromegaly that are treated with somatostatin analogue based treatment regimens. The study will consist of the following periods:

- Screening (up to 6 weeks);
- Treatment Period (up to 13 weeks);
- Follow-up Period (up to 4 weeks).

Therefore, the total study duration for the individual subject is up to 23 weeks.

The study design is displayed in Figure 1 and Figure 2

Figure 1 - Screening Period

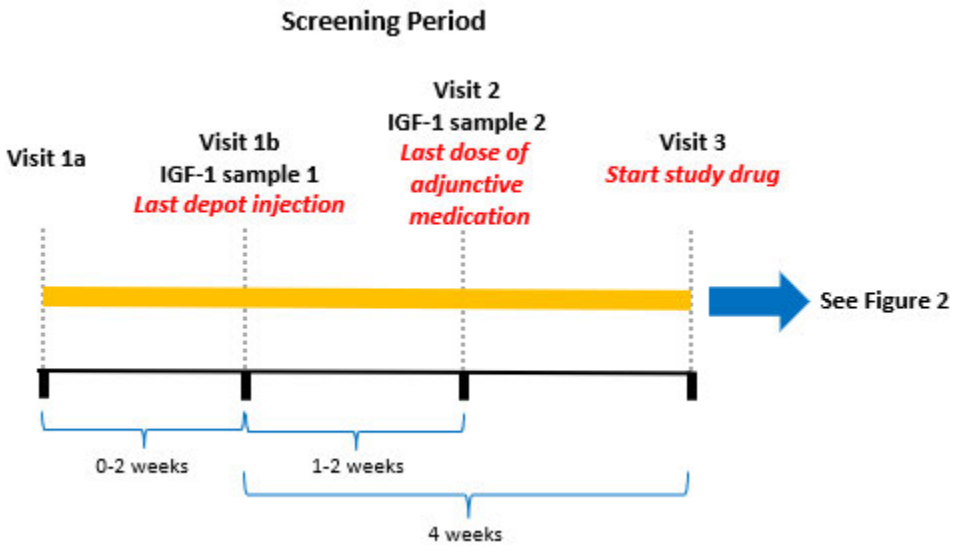
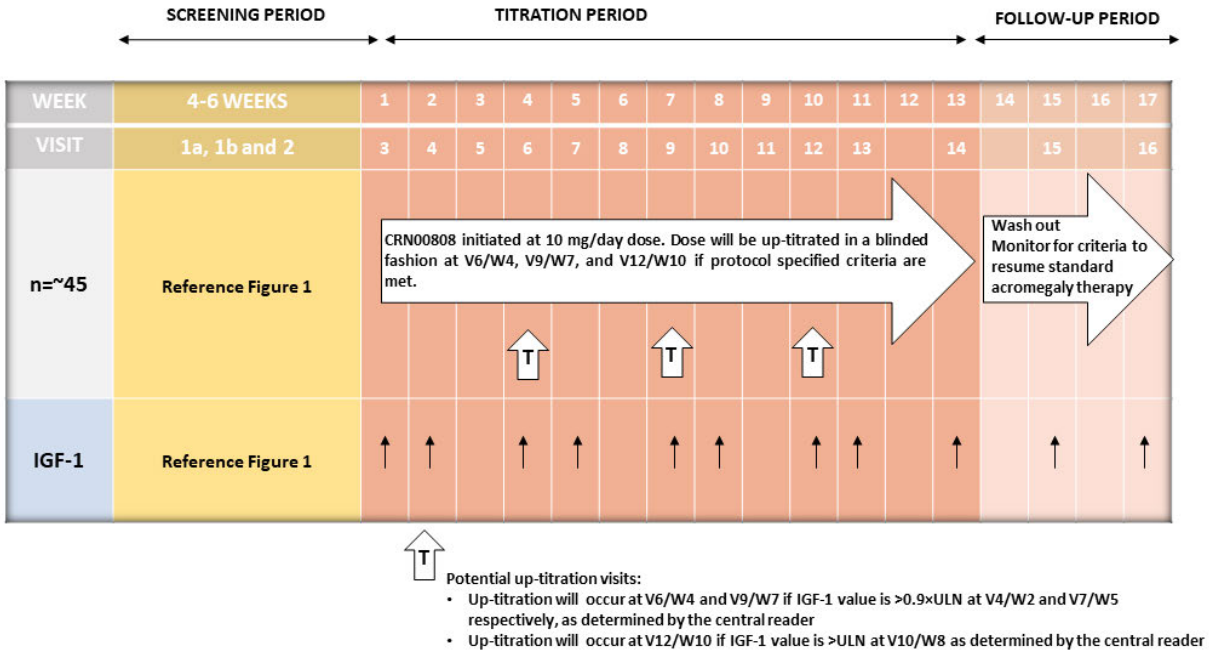


Figure 2 - Overall Study Design



Approximately 45 subjects on stable doses of SSA based pharmacotherapy for the treatment of acromegaly will be recruited for this clinical trial.

Subjects will not be allowed to change their routine exercise regimen during the course of the study.

SCREENING PERIOD

The purpose of the 4-6 week Screening Period is to perform all investigations required to establish a subject's eligibility for the study. Once all assessments are completed and eligibility of the subjects are verified by the Investigator and confirmed by Medical Monitor (MM), the subject will be enrolled in the Treatment Period of the study.

Informed and written consent will be obtained from the subjects at Visit 1a (V1a) prior to any study specific procedure. Eligibility for enrollment into the Treatment Period of the study will be in part determined by two IGF-1 values measured during the Screening Period. The first measurement will occur at V1b (0-2 weeks after V1a) and will be drawn immediately prior to the subjects regularly scheduled dose of octreotide LAR, lanreotide depot or pasireotide LAR. The second IGF-1 measurement will be performed at V2, which will occur 1-2 weeks after V1b.

In order to be eligible to enter the Treatment Period, the Screening IGF-1 measurements (performed by the study central laboratory) must fall into the ranges specified for one of the following groups:

- **Group 1:** Partial responders on a stable treatment of octreotide LAR or lanreotide depot (at least one Screening IGF-1 value must be >ULN, and the V2 value must be ≤2.5×ULN);
- **Group 2:** Partial responders on a stable combination treatment of SSA (i.e., octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (at least one Screening IGF-1 value must be >ULN, and the V2 value must be ≤2.5×ULN);
- **Group 3:** Complete responders on a stable combination treatment of SSA (i.e., octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (mean of Screening IGF-1 values must be ≤ULN);
- **Group 4:** Complete responders on a stable dose of pasireotide LAR (mean of Screening IGF-1 values must be ≤ULN);
- **Group 5:** Complete responders on a stable combination treatment of SSA (i.e., octreotide LAR or lanreotide depot) and pegvisomant (mean of Screening IGF-1 values must be ≤ULN).

A washout (i.e., demonstration of increased IGF-1 levels and/or return of symptoms) before switching from parenteral to oral therapy is not required.

For additional details on screening procedures, refer to Section 5.1 and Table 1.

TREATMENT PERIOD

During the 13-week Treatment Period, subjects will attend 12 study visits which include study drug dispensing, blood sample collection, safety assessments, and other study procedures as indicated in Table 1. The Treatment Period starts with the first dose of study drug ([redacted] for all subjects) at V3, which occurs approximately 4 weeks after V1b, when the last dose of standard acromegaly treatment was administered. Subjects enrolling into the Treatment Period will not continue their standard acromegaly treatment until study completion or early termination. While in the Treatment Period, the subjects will self-administer the study drug at approximately the same time in the morning, once daily after an overnight fast of at least 6 hours. Fasting will continue for at least two hours post-dose. At visits V3/W1, V6/W4, V9/W7, V12/W10, and V14/W13 the study drug is to be administered at the study center, also under fasting conditions. During the entire Treatment Period, the subjects are expected to swallow four capsules (Size 2) with water every day.

During the V6/W4 and V9/W7, the dose may be titrated up in a blinded fashion, provided the preceding IGF-1 values collected in V4/W2, and in V7/W5, respectively, are >0.9×ULN and the current dose is tolerated by the subject. At V12/W10, the dose may be titrated up in a blinded fashion, provided the preceding IGF-1 value collected in V10/W8 is >ULN and the current dose is tolerated by the subject.

The investigator will assess whether the subject is tolerating the current dose and is blinded to IGF-1 results. The central IGF-1 reader will have access to the unblinded IGF-1 data and will determine if the IGF-1 results meet criteria for potential increase in study drug dose. The Investigator will confirm the subject is eligible for an increase in the study drug dose based on

tolerability at V5/W3, V6/W4, V8/W6, V9/W7, V11/W9 and V12/W10. If tolerability is confirmed and the IGF-1 reader has determined that IGF-1 has not met adequate suppression criteria, a blinded blister card containing the appropriate higher dose will be assigned at the V6/W4, V9/W7 and/or V12/W10. Dose increases in [redacted] increments will be allowed only at the V6/W4 (from [redacted] V9/W7 (from [redacted]) and V12/W10 (from [redacted]). No further up-titrations will be allowed. The daily dose will not exceed [redacted].

If IGF-1 suppression as defined above has been achieved with a tolerated dose, the dose will not be changed. At any time during study drug dosing, including at V6/W4, V9/W7 and V12/W10, study drug dosing may be reduced in a blinded fashion on one occasion if the investigator determines that the subject is not adequately tolerating the study drug. In general, a suspected CRN00808-related AE sufficient to result in a study drug dose reduction would be expected to be of Grade 3 (Severe) intensity.

An unblinded CRO designate will oversee the correct assignment of new blinded dose blister cards taking into account information from the investigator and from the central IGF-1 reader.

Subjects will return to the study center at the end of W13 (i.e., V14) on the last day of dosing. No further treatment with the study drug will be allowed after completion of V14/W13.
For other details and procedures performed during Treatment Period, refer to Section 5.2 and Table 1.

Dose Decreases During Treatment Period

At any point during the Treatment Period of the study, subjects treated with [redacted] per day who are judged by the investigator as intolerant of the current dose of the study drug should undergo a one-time dose reduction ([redacted]). Initiation of the lower dose may be preceded by up to a 7-day interruption in the study drug dosing as clinically appropriate. In subjects whose dose is reduced from [redacted] per day, a resumption of [redacted] per day may be allowed at the next up titration adjustment opportunity visit (V6/W4, V9/W7 and/or V12/W10) if IGF-1 control is inadequate while taking [redacted] per day and the subject is tolerating the [redacted] dose well. If in the judgement of the investigator, the subject is eligible for a re-challenge at the higher dose at an up-titration visit, subjects who have been dose reduced from [redacted] may re-challenge at [redacted] respectively. Subjects whose dose is reduced from [redacted] per day will not be allowed to re-challenge with the [redacted] dose.

The Investigator will be responsible for communicating the need for a dose decrease to the unblinded CRO delegate. The CRO delegate will oversee the correct assignment of the appropriate dose blister card containing the new dose.

FOLLOW-UP PERIOD

During this 4-week-period subjects will attend 2 study visits (V15/W15 and V16/W17) and are expected to be off any acromegaly treatment, including CRN00808.

For other details and procedures performed during the Follow-up Period, refer to Section 5.3 and Table 1.

Criteria for Resumption of Standard Acromegaly Treatment

At any time during the Treatment Period, if the subject is experiencing a significant worsening of symptoms associated with acromegaly, and in the Investigator's opinion would not benefit from continuing in the study, standard acromegaly treatment should be resumed. Subjects meeting these criteria will be discontinued from the study and an early termination visit will be scheduled, prior to resuming standard pharmacotherapy whenever possible. For purposes of this determination, symptoms include those defined in Section 6.1.11 and others at the discretion of the Investigator. "Significant worsening" in the opinion of the Investigator may be defined as symptoms requiring a substantial increase in level of clinical care (e.g., significant intervention needed to avert hospitalization or clinically notable increase in frequency or intensity of patient contact required) or substantial clinical deterioration (e.g., worsening from a mild to severe AE or the onset of an SAE would meet this criteria).

During the Follow-up Period, standard acromegaly treatment should be resumed if the subject experiences significant worsening of acromegaly symptoms (as defined above) and the most recent IGF-1 value is >ULN. Such subjects should have V16 performed prior to resumption of standard acromegaly treatment whenever possible. These subjects will be considered study completers.

3.2 Study Population

Approximately 45 male and female subjects with a confirmed acromegaly diagnosis who fall into one of the five groups are planned to be enrolled in this study.

- **Group 1:** Partial responders on a stable treatment of octreotide LAR or lanreotide depot (at least one Screening IGF-1 value must be >ULN, and the V2 value must be ≤2.5×ULN);
- **Group 2:** Partial responders on a stable combination treatment of SSA (i.e., octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (at least one Screening IGF-1 value must be >ULN, and the V2 value must be ≤2.5×ULN);
- **Group 3:** Complete responders on a stable combination treatment of SSA (i.e., octreotide LAR or lanreotide depot) and a dopamine agonist (bromocriptine or cabergoline) (mean of Screening IGF-1 values must be ≤ULN);
- **Group 4:** Complete responders on a stable dose of pasireotide LAR (mean of Screening IGF-1 values must be ≤ULN);
- **Group 5:** Complete responders on a stable combination treatment of SSA (i.e., octreotide LAR or lanreotide depot) and pegvisomant (mean of Screening IGF-1 values must be ≤ULN).

Groups 1 and 2 will contribute at least 30 of the approximately 45 subjects enrolled.

The subject's eligibility will be verified by the Investigator and confirmed by the Medical Monitor before entry into the Treatment Period.

3.2.1 Inclusion Criteria

Subjects must meet all the following criteria to be eligible for entry into the Treatment Period:

1. Medically stable male and female subjects 18 to 75 years of age, inclusive, with a confirmed acromegaly diagnosis, who meet the protocol defined criteria (see Section 3.2) for a partial or complete responder to somatostatin analogue based therapy. A stable dose is defined as no changes in acromegaly medication doses in the last 3 months;
2. Diagnosis of active acromegaly confirmed by the Investigator and approved by the Medical Monitor. At a minimum, there must be a documentation available of a pituitary tumor and elevated IGF-1 in the past. In subjects who have undergone pituitary surgery, elevated IGF-1 measured three or more months after surgery must be documented. A head MRI (or CT Scan for subjects unable to undergo MRI) with pituitary imaging will be performed during the Screening Period unless recent documented scan performed within 6 months prior to Screening is available;
3. Subjects with hypothyroidism must be on stable treatment for at least 3 months with normal free T4 levels and should be clinically euthyroid at Screening as determined by the investigator;
4. Subjects with adrenal insufficiency must be on adequate adrenal replacement therapy at the time of Screening as determined by the investigator;
5. If the subject is female, she must be of non-childbearing potential (defined as either surgically sterilized [i.e., hysterectomy, bilateral salpingectomy, or bilateral oophorectomy] or at least 1 year of amenorrhea) OR must agree to use highly effective or two clinically acceptable methods of contraception from the beginning of Screening to the last study visit.
    - Acceptable highly effective methods of contraception include intrauterine device (IUD); intrauterine system (IUS); bilateral tubal occlusion (must be documented); non-oral hormonal contraceptives; desogestrel-based progestin-only oral contraceptives; vasectomized partner (must be documented); or sexual abstinence (only when it is the usual and preferred lifestyle of the subject). Clinically acceptable methods of birth control include male or female condom with or without spermicide; norethindrone-based progestin-only oral contraceptives; or cap, diaphragm, or sponge with spermicide. Note that simultaneous use of male and female condoms with or without any other contraception methods is not permitted. Oral hormonal contraceptives containing estrogens are not permitted.
6. If the subject is male, the subject must use a condom, or his female partner of childbearing potential must use an effective form of contraception as described above, from the beginning of Screening to the last study visit. Male subjects must also agree not to donate sperm for the duration of the study and until at least 3 months after the last dose of the study drug;

7. Subjects must be willing and able to comply with the study procedures as specified in the protocol and comply with the study treatment;
8. Negative results on a test for the following drugs during Screening: amphetamine, barbiturates, cocaine, methamphetamine, methadone, opiates, phencyclidine, and methylenedioxymethamphetamine;
9. Written Informed Consent provided prior to any study related procedures.

3.2.2 Exclusion Criteria

Subjects meeting any of the following criteria will be ineligible to participate in the study:

1. Treatment naïve acromegaly subjects;
2. Acromegaly subjects who had pituitary surgery within 6 months prior to Screening or subjects in Group 3, 4, or 5 who have undergone pituitary radiation therapy at any time prior to the study entry. A history of radiation therapy is not a restriction for subjects in Group 1 or 2. If a subject in Group 3, 4, or 5 has undergone pituitary radiation therapy ≥4 years prior to Screening and has had a documented IGF-1 ≥1.3×ULN within 2 years prior to Screening OR if a subject has undergone pituitary radiation therapy between 3 and 4 years prior to Screening and has had a documented IGF-1 ≥1.3×ULN within 1 year prior to Screening, the subject may be included in the study;
3. Subjects with any clinically significant concomitant disease including but not limited to cardiovascular disease; moderate or severe renal insufficiency (eGFR<60 mL/min/1.73 m^2); or significant liver disease (including cirrhosis);
4. History or evidence of any of the following within the previous 6 months: myocardial infarction, cardiac surgery revascularization (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty), cerebrovascular accident or stroke or transient ischemic attack (TIA). Syncope or marked presyncope that is unexplained or related to cardiovascular disease within the last 5 years;
5. Any of the following conditions: personal history of cardiac arrest or long QT syndrome, evidence for a familial sudden death syndrome, hemodynamically significant cardiac valvulopathy, greater than Canadian Cardiovascular Society Class 1 angina pectoris or unstable angina, greater than NYHA Class 1 congestive heart failure, ongoing episodes of symptomatic bradycardia (i.e., bradycardia associated with significant dizziness, lightheadedness, or loss of consciousness), known history of sustained ventricular tachycardia, hemodynamically significant pulmonary arterial hypertension; uncontrolled symptomatic supraventricular tachycardia, uncontrolled atrial fibrillation (chronic persistent atrial fibrillation that is appropriately rate controlled and anticoagulated is acceptable for inclusion), type 2 second degree or third degree atrioventricular block;
6. Based on Holter monitor performed during the Screening Period: symptomatic bradycardia (i.e., bradycardia associated with significant dizziness, lightheadedness, or

loss of consciousness), type 2 second degree or third degree atrioventricular block, pause >3 sec, sustained ventricular or supraventricular tachycardia, previously undiagnosed paroxysmal atrial fibrillation, or torsades de pointes;

7. Supine systolic blood pressure >150 mmHg and/or supine diastolic blood pressure >95 mmHg at Screening (if the initial measurement is out of range, may be repeated 2 more times after 15 min and exclusion will be based on the average of the three measurements);
8. Resting (at least 10 minutes) palpated pulse rate <50 bpm or >105 bpm at Screening. If either of these criteria are met, the assessment should be repeated 2 more times and the average should be used to determine the subject's eligibility;
9. QTcF interval >450 msec (or QTc >480 msec in the presence of a bundle branch block) or PR interval >240 msec at Screening based on a central reading of an average of 3 ECGs each separated in time by approximately 1 minute after the subject has rested supine for at least 10 minutes;
10. Currently receiving medications that are known to be associated with torsades de pointes (Appendix 2 - Medications Associated with Torsades De Pointes);
11. Currently receiving medications that are known to cause heart rate slowing (beta-blockers, verapamil, diltiazem, or ivabradine) if resting heart rate at Screening is <60 bpm;
12. Currently receiving medications that are strong inducers of CYP3A4 or inhibitors of CYP3A4 (see Protocol Section 4.7.2);
13. Subjects with autonomic disease (caused by diabetes or Parkinson's disease);
14. Subjects with symptomatic cholelithiasis;
15. Subjects with amylase and/or lipase levels >2×ULN, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2×ULN, total bilirubin >1.5×ULN (except when there is known Gilbert's Syndrome) and/or creatinine >1.5×ULN at Screening. Subjects with previously diagnosed Gilbert's syndrome not accompanied by other hepatobiliary disorders and associated with total bilirubin <3 mg/dL (<51.3 µmol/L) and direct bilirubin ≤ULN will be permitted;
16. Subjects who are complete responders (both Screening IGF-1 values ≤ULN) to octreotide LAR or lanreotide depot monotherapy;
17. Subjects taking octreotide LAR at a dose higher than 40 mg, or lanreotide depot at a dose higher than 120 mg, or pasireotide LAR higher than 60 mg;
18. Subjects who usually take octreotide LAR, lanreotide depot or pasireotide LAR less frequently than every 4 weeks (e.g., every 6 weeks or 8 weeks);
19. Subjects who have undergone major surgery/surgical therapy for any cause within 4 weeks prior to Screening;
20. Subjects with poorly controlled diabetes mellitus defined as having a $HbA1_c$ ≥8.5% (69 mmol/mol);

21. Subjects with diabetes treated with insulin for less than 6 weeks prior to the study entry, or with an unstable insulin dose in 6 weeks prior to the study entry;
22. Subjects with clinically significant abnormal findings during the Screening Period, and any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardize the subject's safety or ability to complete the study;
23. Female subjects who are pregnant or lactating. Absence of pregnancy will be confirmed by serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a negative urine hCG pregnancy test at V3 prior to drug administration;
24. Subjects with hepatitis B, Human Immunodeficiency Virus (HIV), or hepatitis C infection. Subjects with previous hepatitis C infection that is now cured may be eligible;
25. Subjects with known history of, or current alcohol or drug abuse, within the last 12 months;
26. Subjects with any mental condition rendering him/her unable to understand the nature, scope and possible consequences of the study, and/or evidence of poor compliance with medical instructions;
27. Subjects with a known allergy or hypersensitivity to any of the test materials or related compounds;
28. Subjects who have been treated with proton pump inhibitors and/or H2 blockers within 2 weeks prior to Screening;
29. Subjects with active malignant disease within the last 5 years with exception of basal and squamous cell carcinoma of the skin with complete local excision and resected carcinoma in situ of cervix;
30. An employee or immediate family member of an employee of Crinetics;
31. Participation in any previous trial with CRN00808, except for subjects who have screen failed study CRN00808-02;
32. Subjects who have been dosed with an investigational drug (either approved or not approved) in any prior clinical study within 30 days or 5 half-lives (whichever is longer) prior to Screening.

3.2.3 Withdrawal, Removal, and Replacement of Subjects

All subjects will be informed that they have the right to withdraw from the study at any time, for any reason, without prejudice, and without having to justify their reasons or decisions. Additionally, the investigator may discontinue subject's participation at any time if he/she considers that to be in the subject's best interest or if the investigator determines that continuing the participation would result in a significant safety risk for that subject. A discontinuation of treatment occurs when an enrolled subject discontinues participation in the study, regardless of the circumstances, prior to completion of the study. However, every effort should be made to observe subjects who have been enrolled until the scheduled end of their observation without study discontinuation, even if they discontinue early from the study drug treatment. However,

if subjects meet criteria for resumption of standard acromegaly treatment or if they require initiation of a prohibited concomitant medication during the Treatment Period, they will need to discontinue from the study.

In case of early discontinuation of study participation, the investigator should schedule an early termination visit, particularly to ensure collection of AE follow-up data (if applicable) and to collect samples for laboratory evaluations. This visit should be documented in the appropriate electronic Case Report Form (eCRF). The investigator will record the reason for the study discontinuation and provide or arrange for appropriate follow-up and ensure return to standard acromegaly treatment for such subject. In addition, the investigator will report the subject's withdrawal to the responsible MM within 24 hours.

Reasons for a subject to discontinue the study treatment and/or participation in this clinical study include but are not limited to:

1. Withdrawal of informed consent by a subject;
2. Occurrence of adverse events for which study treatment and/or study participation discontinuation is desired by the subject or considered necessary by the investigator or the MM;
3. Indication of clinically significant cardiac symptoms or findings (see Section 6.1.7):
    a. Based on the average of triplicate ECGs, QTcF >500 msec (or QTc >530 msec in subjects with a bundle branch block) repeated on a second set of ECGs at least 2 hours apart and confirmed by a stat central ECG reading;
    b. Any ventricular tachyarrhythmia associated with symptoms of hemodynamic response;
    c. Sustained ventricular tachycardia (lasting >30 sec) irrespective of symptoms;
    d. Torsades de pointes;
    e. Cardiac arrest;
    f. Pause >5 sec;
    g. Type 2 second degree block or third degree AV block;
    h. New occurrence of clinically significant, symptomatic bradycardia;
    i. An increase in QTcF >75 msec with an absolute QTcF <500 msec (confirmed by the central ECG laboratory);
    j. Initiation of a concomitant medication during the Treatment Period which prolongs the QT interval (regardless of association with torsades de pointes). Medications associated with torsades de pointes (as listed in Appendix 2 - Medications Associated with Torsades De Pointes) are exclusionary during the screening process and are not allowed as a concomitant medication at any time during the study (see Section 4.7.2);
    k. Any supraventricular tachyarrhythmia associated with symptoms of hemodynamic response.
4. Indication of drug-induced liver injury:

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

5. Other clinically significant drug-related abnormalities (e.g., newly developed or worsening hyperglycemia, hypersensitivity, symptomatic cholelithiasis, pancreatitis);
6. Investigator's decision (i.e., if in the investigator's opinion it is not in the best medical interest for the subject to continue participation in the study for reasons other than AEs);
7. Need for administration of a non-permitted concomitant medication;
8. Any other protocol deviation that may result in a significant risk to the subject's safety or protocol deviations that will interfere with assessment of the efficacy endpoints of this study, including subject's non-compliance with the study procedures/study protocol;
9. Pregnancy;
10. Lost to follow-up (the subject stopped coming for visits, and study personnel are unable to contact the subject);
11. Inability to fulfil study requirements and procedures;
12. Death.

Groups 1 and 2 will contribute at least 30 subjects. Once this is achieved, subjects withdrawn from the study will NOT be replaced.

3.2.3.1 Termination of Study Participation

If early study termination is necessary, discontinuation of a subject from the study should be discussed with MM in order to plan the transition to a standard treatment. Adverse events related to the study drug will be followed for outcome information until resolution or stabilization.

3.2.4 Follow-Up for Drug Discontinuation/Subject Withdrawal from the Study

If a subject discontinues or is permanently discontinued from study drug treatment, the investigator should:

- Record withdrawal reason in the eCRF;
- Complete Early Termination Visit (i.e., V16). Whenever possible, this should occur prior to resumption of standard acromegaly therapy. Refer to Section 5.3.

If a subject fails to attend scheduled assessments, the investigator must determine the reasons and the circumstances as completely and accurately as possible.

If a subject is discontinued from the treatment due to an AE, the investigator will arrange proper follow-up with the subject at his/her discretion until the event has been resolved or stabilized.

For subjects who are lost to follow-up (i.e., subjects whose status is unclear because they fail to appear for the study visits without stating an intention to withdraw), the investigator should document in the source documents all steps taken to contact the subject (e.g., dates of telephone calls, registered letters).

Subjects who withdraw the informed consent will not have further information or data collected from them, with the exception of follow-up information about AEs related to the Investigational Medicinal Product (IMP) that are ongoing at the time of withdrawal. Every effort will be made to follow up subjects who are withdrawn from the study for SAEs considered related to the IMP.

If a withdrawal is caused by a Suspected Unexpected Serious Adverse Reaction (SUSAR), it will be reported to the Regulatory Authorities and Institutional Review Boards/Independent Ethics Committees (IRBs/IECs).

3.2.5 Discontinuation of the Study

The Sponsor reserves the right to discontinue the study at any time for any appropriate reason. Such reasons may include, but are not limited to, the following:

- Inefficacy of the study medication;
- Results from ongoing safety monitoring;
- Other medical or ethical reasons.

Regulatory Authorities also have the right to terminate the study for any reason.

In the event the study is terminated, the IRB/IEC and Competent Authority will be notified of the relevant decision.

4 TREATMENT PROCEDURES

4.1 CRN00808 (Investigational Medicinal Product)

CRN00808 is an orally administered nonpeptide somatostatin agonist that is expected to lower serum IGF-1 and GH levels in acromegaly patients.

[redacted] is the active pharmaceutical ingredient.

[redacted] is available as [redacted] ([redacted] Size 2) and [redacted] ([redacted] Size 2) solid dose capsules.

The IMP contains the following excipients: [redacted]. These excipients are commonly used in solid oral formulations and are Generally Regarded as Safe and are found on the FDA Interactive Ingredient Guide (IIG) list.

The [redacted] capsules are packaged in PVC blisters and stored at [redacted].

4.2 Packaging and Labeling

Capsules ([redacted], and matching placebo) will be supplied in blisters containing 36 capsules each.

The capsules will be manufactured, packaged and labelled according to the principles of Good Manufacturing Practices (GMP) and applicable regulatory requirements of each country.

The study drug labels will be printed in local languages and the label content will comply with GMP, Annex 13 to GMP-Guideline "Manufacture of Investigational Medicinal Products" as well as specific requirements of each country. The Pharmacy Manual contains all the details and instructions for labelling, storage and handling of the IMP and reference. The storage conditions for the study drug will be described on the medication label as well.

4.3 Treatment Assignment and Blinding

Subjects who are determined to be eligible to enter the study drug Treatment Period will all begin treatment with CRN00808 at [redacted] per day. All subsequent dose changes will be blinded.

4.4 Method of Administration

4.4.1 CRN00808 Dosing and Administration

CRN00808 will be taken once a day in the morning after an overnight fast (at least 6 hours). The subjects must swallow four capsules (Size 2) with water every day. No food will be allowed for at least 2 hours after drug administration including time of the study drug administration.

Subjects should avoid exposure of skin or eyes to direct sunlight or UV light for the duration of the study and for at least 10 days after receiving the last dose of study drug.

Refer to Section 3.1 for dose titration instructions.

Subjects will be provided with daily diaries in which to record confirmation of fasting prior to dosing and for two hours after dosing including the time of the study drug administration; time of last meal prior to study drug administration; and time of meal following fasting.

For details regarding the study drug administration, refer to Pharmacy Manual.

Additional information about the study drug is provided in the current version of the IB.

4.4.2 Background Medication

Subjects will receive their final pre-trial acromegaly medications (octreotide LAR, lanreotide depot, pasireotide LAR, dopamine agonist or pegvisomant) for use during the Screening Period. At V1b, the subject will receive the final injection of the somatostatin agonist (octreotide LAR, lanreotide depot, or pasireotide LAR) approximately 4 weeks prior to entry into the Treatment Period of the study (V3). For subjects previously treated with adjunctive dopamine agonist or pegvisomant, the last dose of the adjunctive medication will be administered at V2.

4.5 Study Drug Supply, Storage and Tracking

Study drug must be received by the appointed study staff at the study site that will take all steps to maintain adequate records and will ensure that the study drug is stored as specified on the medication labels, in a strictly controlled, secure area, at appropriate temperature and in accordance with the protocol and any applicable regulatory requirements. Clinical supplies will be provided by the Sponsor and are to be dispensed only in accordance with the protocol.

An accurate inventory and accountability records of the study drug will be kept by the appointed team member.

All drug supplies will be provided by the Sponsor and the logistics of supply would be managed by the Sponsor/appropriate designee. The study drug will be provided with appropriate labelling.

The capsules are to be stored at [redacted]

All study drug should be stored and inventoried according to applicable state and federal regulations and study procedures.

At the end of the study (i.e., close-out visit) and following reconciliation and documentation by the site monitor, all study drugs and related materials will be either returned to the Sponsor or a designee, or destroyed locally following the review and approval of the site's destruction procedures.

The study drugs (sufficient to last until the next planned visit) will be dispensed by the appointed study staff to the subjects at relevant study visits and should be stored at [redacted], out of reach of children. The storage conditions will be carefully described to the subjects.

Full details concerning accountability, tracking and recording will be provided in a Pharmacy Manual.

4.6 Drug Accountability and Treatment Compliance

The appointed team members will be identified at each center whose role in the study will be handling of the study drugs (i.e., they will be responsible for the receipt and accountability of the study drug). Furthermore, other tasks can be delegated to them in a clear manner by the Principal Investigator and that will be documented and completed in the *Study Staff Signature Verification Form*.

Records of the study drugs used, dosages administered, and intervals between visits will be kept during the study. Further details are provided in the Pharmacy Manual and relevant monitoring plan.

Subjects will be instructed to return all used and unused study drugs at each study visit during the Treatment Period. A compliance check will be performed by counting the capsules returned at each study visit. All returned study drug and study drug materials should be stored, inventoried, reconciled, and returned according to applicable local regulations and study procedures.

4.7 Medical History and Prior/Concomitant Medications

The investigator should document medications, medical conditions, prior illnesses with diagnosis(es), surgeries, allergies that the subject has experienced before the study entry, i.e., before signing ICF, as well as ongoing illnesses in the eCRF Medical History Page. Additional illnesses present from the time when ICF is signed and up to the end of the study are to be documented as AEs on the eCRF Adverse Event Page.

Prior medication/therapy (i.e., any therapy given within 3 months before signing Informed Consent) and each medication/therapy that is ongoing will be recorded in the eCRFs Prior/Concomitant Medications or Non-Pharmacological Treatment Page.

Concomitant therapy is considered any medication other than the investigational or reference product that is administered at any time from the first day of the study medication administration until the end of the study. For details refer eCRF completion guideline.

In case a new concomitant therapy becomes necessary during the study, this must be documented and appropriately listed within the Prior/Concomitant Medications or Non-Pharmacological Treatment Page in the eCRF.

Any change in concomitant medication after signing the ICF must be recorded in the eCRF, noting the type of medication, the dose, route, duration, and indication. If during the study drug treatment period, the administration of a prohibited concomitant medication (see below) is deemed to be medically necessary, the subject will need to discontinue from the study.

All subjects should agree to the following restrictions during the study:

- Not to start any new prescription medication, except as prescribed or approved by the investigator or if required in an emergency;

- Not to start any over-the-counter medication, homeopathic preparations, or herbal supplements, except as instructed or approved by the investigator.

4.7.1 Permitted Concomitant Medications

Concomitant medications allowed in this study are those non-prohibited medications used at Screening to control existing medical conditions and/or those initiated during the study if medically needed. All concomitant medications will be recorded in the subject's medical file and on the appropriate eCRF page. If a new medication should become necessary for any reason during the course of the study, the subject is required to inform the Investigator immediately, who will record the drug, the dose and the time of administration in the subject's eCRF.

4.7.2 Prohibited Concomitant Medications

Any questions regarding prohibited medications should be discussed with the Medical Monitor or appropriate designee.

- Oral estrogens (including estrogen-containing oral contraceptives);
- Proton pump inhibitors, H2 blockers;
- OTC antacids ([alkali based that directly neutralize hydrogen ions] or other drugs that can inhibit gastric acid secretions shall be restricted 4 hours before and after administration with CRN00808);
- Strong inducers of the drug metabolizing enzyme CYP3A4, including but not limited to: carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort;
- Strong inhibitors of the drug metabolizing enzyme CYP3A4, including but not limited to: boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir;
- Any drug that is used for the treatment of acromegaly including but not limited to octreotide, lanreotide, pasireotide, cabergoline, bromocriptine, pegvisomant;
- QT-prolonging drugs known to be associated with torsades de pointes (as listed in Appendix 2 - Medications Associated with Torsades De Pointes). Drugs that are associated with QT interval prolongation regardless of listed association with torsades de pointes or drugs that cause heart rate slowing should prompt study drug cessation and discussion of the case with the Medical Monitor within 24 hours (see Section 6.1.7);
- Medications that are known to cause heart rate slowing (e.g., beta-blockers, verapamil, diltiazem, or ivabradine) may be started during the study if resting pulse is ≥60 bpm and if approved by the Medical Monitor. An unscheduled ECG should be performed approximately 5 days after starting the new medication to assess HR and QTcF.
- Any other investigational drug.

4.8 Contraception

If the subject is female, she must be of non-childbearing potential (defined as either surgically sterilized [i.e., hysterectomy, bilateral salpingectomy, or bilateral oophorectomy] or at least 1 year of amenorrhea) OR must agree to use highly effective or two clinically acceptable methods of contraception from the beginning of Screening to the last study visit.

Acceptable highly effective methods of contraception include intrauterine device (IUD); intrauterine system (IUS), bilateral tubal occlusion (must be documented); non-oral hormonal contraceptions; desogestrel-based progestin-only oral contraceptives vasectomized partner (must be documented); or sexual abstinence (only when it is the usual and preferred lifestyle of the subject). Clinically acceptable methods of birth control include male or female condom with or without spermicide; norethindrone-based progestin-only oral contraceptives; or cap, diaphragm, or sponge with spermicide. Note that simultaneous use of male and female condoms with or without any other contraception methods is not permitted. Oral hormonal contraceptives estrogen-containing are not permitted.

If the subject is male, the subject must use a condom, or his female partner of childbearing potential must use an effective form of contraception as described above, from the beginning of Screening to the last study visit. Male subjects must also agree to not donate sperm for the duration of the study and until at least 3 months after the last dose of the study drug.

5 STUDY PROCEDURES

Table 1 outlines the timing of the procedures and assessments to be performed throughout the study. Additional details of the study procedures are given below. Designated visits as noted in Table 1 may be performed either at the study center, via telephone contact, and/or in the subject's home or suitable alternate location by qualified study staff.

5.1 Screening Period (V1a, V1b, V2)

Prior to performing any study-related procedures, the investigator (or his/her designated staff member) will obtain written Informed Consent from the subject.

The Screening Period will last 4-6 weeks in order to collect current clinical data and to perform all required investigations needed to verify subject's eligibility for the study and to obtain baseline data on the subject's acromegaly symptoms. See Section 3.1 for more information about the Screening Period. Note that Visit 1a and Visit 1b may either be combined into a single visit/day or may be separated by as much as two weeks.

During this period, the subject will have at least 2-3 study visits. The following assessments, procedures and data collection will be performed during the Screening Period:

- Obtaining written Informed Consent (V1a) - to be completed before any other study procedure;
- Eligibility verification (V2);
- Medical history/Acromegaly History (V1a);
- Complete physical examination (including weight, height and ring size, at V1a);
- Vital signs (V1a and V2);
- 24-hour-outpatient Holter will be conducted during Screening. An adequate Holter recording should be confirmed by the central laboratory as soon as possible after completion, so that a repeat Holter monitor may be performed, if necessary, prior to Treatment Period;
- 12-lead ECG in triplicate (V1a and V2);
- Serum pregnancy test (applicable only for women of childbearing potential, at V1a);
- HBV, HCV and HIV testing (V1a);
- Assessments of routine safety, hematology and biochemistry (including $HbA1_c$) – non-fasting (V1a);
- Urinalysis (V1a)
- Urine drug screen (V1a);
- Head MRI with pituitary imaging (if a recent documented scan conducted within 6 months of V1a is not available);
- Injection of pre-trial pharmacotherapy (octreotide LAR, lanreotide depot or pasireotide LAR, at V1b)

- Measurement of GH, levels (integrated [set of three values taken at least 30 minutes apart over 2 hours]), *sample set 1*: at V1b (prior to dosing with the depot), *sample set 2*: at V2 (anytime);
- Measurement of IGF-1 levels and [redacted] levels, *sample 1*: at V1b (before the last depot dose); *sample 2*: at V2 (7-14 days after the last depot dose);
- Assessment of hormones (fT3, fT4, thyroid antibody, TSH, cortisol, ACTH, LH, FSH, and prolactin, at V1b before the last dose of depot);
- Residual octreotide/lanreotide/pasireotide plasma sample (V1b before the last deport dose and V2);
- Gall bladder ultrasound completed by V2 (if a recent documented ultrasound within 3 months of V1a is not available);
- Acromegaly baseline investigator assessed symptoms (at the study entry, at V1a ONLY);
- AE assessment (V1a, V1b, and V2), including investigator assessed changes in symptoms of acromegaly (V1b and V2);
- Patient Global Impression of Severity (V1a, V1b, and V2);
- [redacted] (daily beginning the day after V1b through V3);
- Prior and concomitant medication review (V1a, V1b, and V2).

5.1.1 Screening Failures

Subjects who fail to meet the eligibility criteria at any point during the Screening Period are defined as screening failures. The reason for each screening failure will be recorded in the appropriate source document.

Subjects who have screen failed based on findings which are felt by the investigator to be temporary and not reflective of the usual state of the patient (e.g., $HbA1_c$ of >8.5% when the subject is usually well below 8.5%) can be considered for re-screening. These cases should be discussed with the Medical Monitor.

Subjects who screen fail based on their IGF-1 results may be considered for screening in the CRN00808-02 study.

Subjects who have screen failed study CRN00808-02 will be discussed with the medical monitor and when possible, previously obtained screening information may be used for the purpose of eligibility determination for study CRN00808-03. Informed consent for CRN00808-03 is required to be obtained prior to initiating any new CRN00808-03 procedures.

5.1.2 Re-screening

The decision on re-screening will be made on a case by case basis by the PI in consultation with the MM. Re-screened subjects will receive a new subject number. A subject who is re-screened must meet all inclusion and exclusion criteria as part of their re-screening to be eligible for the study. The separate subject numbers for the same subject will be linked.

5.2 Treatment Period

During this 13-week-period, subjects will self-administer the study drug once daily in the morning after an overnight fast [at least 6 hours] and fasting will continue for at least two hours post-dose. The study drug will be administered at approximately the same time. However, the study drug is to be administered at the study center at V3/W1, V6/W4, V9/W7, V12/W10, and V14/W13. The first dosing with the study drug will occur on V3/W1 (approximately 4 weeks following the last depot dose at V1b) after all relevant procedures have been completed. The subjects are expected to swallow four capsules (Size 2) with water every day.

Subjects will not be allowed to change their routine exercise regimen during the course of the study. See Section 3.1 for more information about the Treatment Period.

In case of early termination, all efforts to perform the V16/Early Termination assessments should be taken.

The allowed visit window in the treatment period is ±2 days for most visits. The exceptions are V4, V7, and V10 for which the visit window is +4 days and V14 for which can occur on D90-91. In addition, Visit 7 and Visit 10 must be at least 7 days after Visit 6 and Visit 9, respectively.

During this period there will be 12 study visits when the following assessments, procedures and data collection will be performed:

V3 (W1/D1) prior to the first dosing

- Eligibility verification (inclusion/exclusion criteria);
- Complete physical examination (including weight and ring size);
- Vital signs;
- 12-lead ECG (in triplicate);
- Urine pregnancy test (applicable only for women of childbearing potential);
- Assessments of routine safety, hematology, lipid panel, $HbA1_c$, and biochemistry parameters – to be drawn fasting;
- Urinalysis;
- Genotype blood sample (it will be collected for characterizing UGT1A1 genotype; subjects may opt out of this testing);
- Measurement of IGF-1 levels, *sample 3:* before the first dose of the study drug;
- [redacted] questionnaires;
- Study drug dispense (a 3-week-supply of the [redacted] dose of the study drug sufficient to last until V6; one card/week);
- AE assessment, including changes in symptoms of acromegaly;
- Patient Global Impression of Severity;
- Concomitant medications;
- Study drug administration at the study center.

V4 (W2/D8), V6 (W4/D22), V7 (W5/D29), V9 (W7/D43), V10 (W8/D50), V12 (W10/D64), V13 (W11/D71) and V14 (W13/D90-91)

- Symptom directed physical examination. Ring size should be measured on V14;
- Vital signs;
- 12-lead ECG (in triplicate, ONLY at V4, V7, V10, V13 and V14);
- Urine pregnancy test (ONLY at V6, V9, V12 and V14);
- Assessments of routine safety, hematology and biochemistry parameters – V6, V9, V12, and V14 to be drawn fasting. Additionally, assessment of $HbA1_c$ and lipids at V9 and V14 only;
- Urinalysis;
- Measurement of GH levels (integrated [set of three values taken at least 30 minutes apart over 2 hours]): *sample set 3*: at V4 (1-15 hours post dose), *sample set 4*: at V7 (1-15 hours post dose), *sample set 5*: at V10 (1-15 hours post dose), *sample set 6*: at V13 (1-15 hours post dose), *sample set 7*: at V14/D90-91 (1-8 hours post dose);
- Measurement of IGF-1 levels, *sample 4:* at V4 (1-15 hours post dose); *sample 6:* at V6 (prior to dosing); *sample 7:* at V7 (1-15 hours post dose); *sample 9:* at V9 (prior to dosing); *sample 10:* at V10 (1-15 hours post dose); *sample 12:* at V12 (prior to dosing); *sample 13:* at V13 (1-15 hours post dose); *sample 14:* at V14 on the last day of dosing in W13 (prior to dosing).
- Measurement of [redacted] levels will be done only for *sample 4, sample 7*, *sample 10, sample 13* and *sample 14*;
- PK plasma sample (pre-dose and 2 hours (+/- 15 min) post-dose at V6, V9 and V12; 1-15 hours post-dose at V4, V7, V10, and V13; 1-8 hours post-dose at V14);
- Assessment of hormones (fT3, fT4, thyroid antibody, TSH, cortisol, ACTH, LH, FSH and prolactin - ONLY at V14);
- Gall bladder ultrasound (ONLY at V14);
- Residual octreotide/lanreotide/pasireotide plasma sample (at V9 and V14 ONLY);
- [redacted] questionnaires, only at V14;
- Study drug dispense: V6: TITRATION 3-week-supply (3 cards; one card/week), V9: TITRATION 3-week-supply (3 cards; one card/week), V12: TITRATION 4-week-supply (4 cards; one card/week);
- Study drug return and accountability;
- AE assessment, including changes in symptoms of acromegaly;
- Patient Global Impression of Severity;
- Patient Global Impression of Improvement (ONLY at V14);
- [redacted] (daily beginning the day after V13 through V14 ONLY);
- Concomitant medications;

- Confirmation of tolerability for potential dose up-titration (V6, V9 and V12 only);
- Dose titration decision (ONLY at V6, V9 and V12);
- Study drug administration at the study center (V6, V9, V12, and V14 and ONLY).

V5 (W3/D15), V8 (W6/D36), V11 (W9/D57) – Phone Call Assessment

- AE assessment, including changes in symptoms of acromegaly;
- Patient Global Impression of Severity;
- Concomitant medications;
- Confirmation of tolerability for potential dose up-titration (V5, V8 and V11 only).

5.3 Follow-up Period

During this 4-week-period, subjects are expected to be off all acromegaly treatment, including CRN00808. At the end of this period, all subjects should resume their standard acromegaly treatment as clinically appropriate.

If a subject meets criteria for resumption of standard acromegaly treatment during the Follow-Up Period (see Section 3.1), the subject should undergo V16 procedures prior to resuming standard acromegaly treatment whenever possible. Such subjects will be considered study completers.

The allowed visit window in the follow-up period is ±2 days.

During this period there will be 2 study visits when the following assessments, procedures and data collection will be performed:

V15 (W15/D105 and V16 (W17/D119)

- Complete physical examination (including weight and ring size – ONLY on V16);
- Symptom directed physical examination (ONLY on V15);
- Vital signs;
- 12-lead ECG (in triplicate, ONLY on V16);
- Urine pregnancy test (ONLY on V16);
- Assessments of routine safety, hematology and biochemistry parameters (including $HbA1_c$ and lipid panel at V16 only)_– V16 to be drawn fasting;
- Urinalysis;
- Measurement of GH levels (integrated [set of three values taken at least 30 minutes apart over 2 hours]): *sample set 8*: at V16 or early termination (anytime);
- Measurement of IGF-1 levels, *sample 15:* at V15 (anytime), *sample 16:* at V16 (anytime). Measurement of [redacted] levels will be done only for *sample 16*;
- PK plasma sample;
- [redacted] questionnaires, ONLY at V16;
- AE assessment, including changes in symptoms of acromegaly;

- Patient Global Impression of Severity;
- Patient Global Impression of Improvement (ONLY at V16);
- [redacted] (daily beginning the day after V15 through V16);
- Concomitant medications;
- Re-institute standard acromegaly treatment as clinically appropriate (V16) after all study procedures have been completed.

5.4 Unscheduled visits

Unscheduled visits are those visits that occur between regularly scheduled visits. Reasons for unscheduled visits may include, but are not limited to, follow up of adverse events or abnormal laboratory results. In such cases, the investigator may at his/her discretion arrange for a subject to have an unscheduled visit. The unscheduled visit page in the eCRF must be completed.

Table 1 - Overall Visit Schedule

STUDY PROCEDURES [a]	**SCREENING PERIOD** [b]			**TREATMENT PERIOD**												**FOLLOW-UP PERIOD** [c]	
STUDY WEEKS	W-6 to D0			W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W13	W15	W17
STUDY DAYS	-			D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D90-91	D105	D119
STUDY VISITS	V1a	V1b	V2	V3[d]	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[e]
VISIT WINDOW (DAYS)	[b]			-	+4	Phone ±2	±2	+4 [b]	Phone ±2	±2	+4 [b]	Phone ±2	±2	±2	-	±2	±2
Informed consent	X																
Eligibility verification			X	X													
Medical history (including acromegaly history information)	X																
Full physical examination (including weight and ring size)	X			X													X
Symptom directed physical examination					X		X	X		X	X		X	X	X [v]	X	
Height	X																
Vital signs [f]	X		X	X	X		X	X		X	X		X	X	X	X	X
24-hour outpatient Holter monitor completed and verified [g]	X	X	X	X													
12-lead ECG [h]	X		X	X	X			X			X			X	X		X
Pregnancy test [i]	X (s)			X (u)			X (u)			X (u)			X (u)		X (u)		X (u)
HBV, HCV and HIV testing	X																
Clinical laboratory tests (including urinalysis) [j]	X			X	X		X	X		X	X		X	X	X	X	X
Urine drug screen	X																
Genotype blood sample [k]				X													
Head MRI [l]			X														
Serum GH (integrated) [m]		X_1	X_2		X_3			X_4			X_5			X_6	X_7		X_8
Serum IGF-1/[redacted] [n]		X_1	X_2	X_3	X_4		X_6	X_7		X_9	X_{10}		X_{12}	X_{13}	X_{14}	X_{15}	X_{16}
Injection of pre-trial pharmacotherapy		X															X [u]
Hormone levels (fT3, fT4, thyroid antibody, TSH, cortisol, ACTH, LH, FSH and prolactin)		X													X		
Gall bladder ultrasound completed [o]			X												X		
Pharmacokinetic (PK) plasma sample [p]					X		X	X		X	X		X	X	X	X	X
Residual octreotide/lanreotide/pasireotide plasma sample		X	X							X					X		

STUDY PROCEDURES [a]	**SCREENING PERIOD** [b]			**TREATMENT PERIOD**												**FOLLOW-UP PERIOD** [c]	
STUDY WEEKS	W-6 to D0			W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W13	W15	W17
STUDY DAYS	-			D1	D8	D15	D22	D29	D36	D43	D50	D57	D64	D71	D90-91	D105	D119
STUDY VISITS	V1a	V1b	V2	V3[d]	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16[e]
VISIT WINDOW (DAYS)	[b]			-	+4	Phone ±2	±2	+4 [b]	Phone ±2	±2	+4 [b]	Phone ±2	±2	±2	-	±2	±2
Baseline investigator assessed symptoms of acromegaly [q]	X																
Quality of Life questionnaires [redacted] [w]				X											X		X
Study drug dosing on site [r]				X			X			X			X		X		
Study drug dispense				X			X			X			X				
Return and accountability of study drug [s]					X		X	X		X	X		X	X	X		
Adverse event monitoring (including investigator assessed changes in symptoms of acromegaly) [q]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Global Impression of Severity (PGI-S) [y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess compliance with completion of [redacted] [x]			X	X											X		X
Patient Global Impression of Improvement (PGI-I) [y]															X		X
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirmation of tolerability for potential dose up-titration						X	X		X	X		X	X				
Potential dose up-titration [t]							X			X			X				

Visits at the Study Center: V1a/1b, V3, V6, V9, V12, V14, V16
Phone Call Visits: V5, V8, V11
Visits at Either the Study Center or Subject's Home/Suitable Alternate Location: V2, V4, V7, V10, V13, V15

[a] All study assessments will be conducted at approximately the same time of day, unless otherwise specified.

[b] The Screening Period will consist of 2-3 visits over 4-6 weeks. V1b will occur 0-2 weeks after the initial screening visit V1a. V2 will occur 1-2 weeks after V1b. See Figure 1. V7 and V10 must be at least 7 days after V6 and V9, respectively.

[c] During the Follow-up Period, subjects are expected to be off all acromegaly treatment, including CRN00808. During this period, the subjects will be allowed to complete the study and resume a standard acromegaly treatment if the subject experiences significant worsening of acromegaly symptoms and the most recent IGF-1 value is >ULN. Such subjects should have all the V16 assessments performed prior to the resumption of standard acromegaly treatment whenever possible.

[d] Day 1 is the first day of dosing in Week 1. This will occur approximately 4 weeks after V1b, when the last dose of depot was administered.

[e] Final visit for subjects who have completed the study. In case of early termination, V16 assessments will be performed.

[f] Blood pressure, pulse rate, respiratory rate, and body temperature. All measurements are to be taken at rest.
[g] An outpatient 24-hour Holter monitor recording will be conducted during Screening. An adequate Holter recording should be confirmed by the central laboratory as soon as possible after completion, so that a repeat Holter monitor may be performed, if necessary, prior to Treatment Period.
[h] A standard 12-lead ECG will be performed in triplicate (approximately 1 minute apart) after the subject has rested quietly in the supine position for at least 10 minutes without significant stimulation (noise, TV, etc.). It will be performed at V1a, V2, V3 (pre-dose), V4, V7, V10, V13, V14 and V16 only. When possible, the ECGs should be performed while fasting approximately 2 hours after the study drug dosing.
[i] Applicable only for women of childbearing potential. Serum pregnancy tests (S) will be done at Screening. A urine pregnancy test (U) will be done prior to starting dosing on D1 and other visits as indicated above.
[j] Samples for clinical laboratory tests including hematology, biochemistry, and urinalysis will be obtained after overnight fast except at Screening, V4, V7, V10, V13, and V15 which can be drawn fasting or non-fasting. $HbA1_c$ will be drawn at V1a, V3, V9, V14, and V16/ET only. Fasting lipid profile will be drawn at V3, V9, V14 and V16/ET only.
[k] Blood sample for genotyping will be analyzed and will be collected for the determination of the UGT1A1 genotype. Subjects may opt out of this testing.
[l] Head MRI with pituitary imaging will be performed. A recent documented scan conducted within 6 months of V1a is acceptable. The MRI should be documented at V2 or if necessary as late as Day -1 (prior to the Treatment Period). Pituitary CT scanning may serve as an alternative to MRI for subjects who are not eligible for MRI scanning.
[m] Integrated is defined as three values taken at least 30 min apart over 2 hours. The following serum GH (integrated) samples will be collected: **Screening Period:** *sample set 1*: at V1b (prior to dosing with the depot), *sample set 2*: at V2 (anytime), **Treatment Period:** *sample set 3:* at V4 (collected 1-15 hours post study drug dose), *sample set 4*: at V7 (collected 1-15 hours post study drug dose), *sample set 5*: at V10 (collected 1-15 hours post study drug dose), *sample set 6*: at V13 (collected 1-15 hours post study drug dose), *sample set 7*: at V14/D90-91 (1-8 hours post dose), **Follow-up Period:** *sample set 8*: at V16 or early termination (anytime).
[n] Serum IGF-1 levels will be collected twice during the **Screening Period** *sample 1*: at V1b (before the last depot dose); *sample 2*: at V2 (7-14 days after the last depot dose). Once at **Baseline** *sample 3:* at V3 (before the first dose of the study drug). **Treatment Period**: *sample 4:* at V4 (1-15 hours post study drug dose); *sample 6:* at V6 (prior to dosing); *sample 7:* at V7 (1-15 hours post study drug dose); *sample 9:* at V9 (prior to dosing); *sample 10:* at V10 (1-15 hours post study drug dose); *sample 12:* at V12 (prior to dosing); *sample 13:* at V13 (1-15 hours post study drug dose); *sample 14:* at V14 on the last day of dosing in W13 (prior to dosing). **Follow-up Period**: *sample 15:* at V15 (anytime); *sample 16:* at V16 (anytime). Note: Sample 5, sample 8, and sample 11 collections were eliminated as part of protocol Version 3.0; however, the original numbering of the samples was retained.
[redacted] levels will be measured only for *samples 1 (V1b), 2 (V2), 4 (V4), 7 (V7), 10 (V10), 13 (V13), 14 (V14) and 16 (V16).*
[o] Gall bladder ultrasound is to be performed during Screening (by V2 if a recent documented ultrasound conducted within 3 months of V1a is not available), and at V14.
[p] PK sample should be collected at the following time-points: pre-dose and 2 hours (+/- 15 min) post-dose at V6, V9 and V12; 1-15 hours post-dose at V4, V7, V10, and V13; 1-8 hours post-dose at V14; and anytime on V15 and V16. Dosing times will be recorded in eCRF on the days during the Treatment Period when blood PK samples are collected.
[q] Acromegaly symptoms will be assessed by investigator site staff as described in Section 6.1.11.
[r] Subjects will self-administer the study drug once daily (in the morning after an overnight fast of at least 6 hours and fasting will continue for at least two hours post-dose. The study drug will be administered daily at approximately the same time of day. At visits V3, V6, V9, V12, and V14, the study drug is to be administered at the study center. The subject will record the daily date and time of dosing on the diary provided.
[s] At each study visit during the Treatment Period, a compliance check will be performed by counting the capsules remaining. At study center visits, subjects will return all used and unused study drug.
[t] At V6/W4, V9/W7 and V12/W10 the dose may be up-titrated up in a blinded fashion (see Section 3.1).

[u] As clinically indicated in the judgement of the investigator.
[v] Ring size should be measured at the V14 during symptom directed physical examination.
[w] Quality of Life Questionnaires will be completed by the subject at designated study visits prior to performing other study procedures. See Section 6.1.13.
[x] [redacted] at home on a daily basis beginning the day after V1b through V3; daily beginning the day after V13 through V14, and daily beginning the day after V15 through V16. Please see Section 6.1.12.
[y] PGI-S and PGI-I will be completed by the subject at designated study visits after Quality of Life questionnaires and prior to other study procedures. See Section 6.1.14.

6 SAFETY ANALYSIS

6.1 Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs), including serious adverse events (SAEs), complete physical examination, vital sign assessment, ECG recording, outpatient 24-hour Holter, clinical laboratory results (hematology, biochemistry (including $HbA1_c$), hormone levels, urinalysis, GH and IGF-1 levels, and gall bladder ultrasound.

6.1.1 Adverse Events

An adverse event (AE) is any undesirable sign, symptom or medical condition, whether or not considered drug related and occurring after the moment of signing ICF. Information about all AEs, whether volunteered by the subject, discovered by Investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the AE eCRF page and followed as appropriate.

All medical conditions present prior to the study entry will be documented in the Medical History eCRF. However, medical conditions occurring after the moment of signing the ICF or a worsening of a medical condition present prior to the study entry are to be recorded as AEs.

The investigator is obliged to interview a subject at every visit and clarify/discuss with him/her any abnormality that may indicate any potential AE.

Subjects should be informed that they do not have to wait for scheduled visits to report AEs.

Adverse events will be recorded from after the moment of signing ICF, up to 4 weeks after the last dose of the study medication. All AEs occurring after the study drug administration has started will be considered as Treatment-emergent Adverse Events (TEAEs). Adverse events related to the study drug that are ongoing at the end of the study will be followed for outcome information until resolution or stabilization.

Any AE that occurs in the course of a clinical study must be monitored and followed up until:

- it has resolved;
- laboratory abnormalities have returned to normal;
- steady state of the symptoms has been achieved.

It is the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

As far as possible, each AE will also be described by:

- its duration (start and end dates);
- the severity grade;
- its relationship to the study drug;
- the action(s) taken;
- the outcome.

If there is a change in severity of an AE, it must be recorded as a separate event. Any change in severity should be recorded in the source data and eCRF accordingly until a stop date is provided.

Specific guidelines for classifying AEs by intensity and relationship to the IMP are given in Table 2 and Table 3.

Table 2 - Classification of Adverse Events by Intensity

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated (AE is transient and easily tolerated by the subject)
Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental daily activities (AE causes the subject discomfort and interrupts the subject's usual activities)
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care daily activities

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed as severe. An event is defined as “serious” when it meets 1 of the pre-defined outcomes as described below in Protocol Section 6.1.2.

The following judgments of the causal relationship are to be used as described in Table 3.

The investigator will assess any causal relationship of an AE with respect to the IMP.

Table 3 - Classification of Adverse Events by Relationship to Investigational Medicinal Product

NOT RELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the IMP, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to the IMP if or when it meets two of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the IMP; (2) it could readily have been produced by the subject’s clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the IMP; or (4) it does not reappear or worsen when the IMP is re-administered.
POSSIBLY: This category applies to those AEs for which a connection with the IMP administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets two of the following criteria: (1) it follows a reasonable temporal sequence from administration of IMP; (2) it could not readily have been produced by the subject’s clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the IMP.

PROBABLY: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the IMP. An AE may be considered probably related if or when it meets three of the following criteria: (1) it follows a reasonable temporal sequence from administration of the IMP; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the IMP, yet drug-relatedness clearly exists (e.g., as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the IMP.
DEFINITELY: This category applies to those AEs that the investigator feels are incontrovertibly related to the IMP. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the IMP; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to the IMP (if re-challenge occurs); and (4) it follows a known pattern of response to the IMP.

AE outcome

If the same AE occurs several times in the same subject, then the AE in question must be documented and assessed as a new event for each new occurrence unless the event is considered to be a continuation of the previously reported event rather than reoccurrence of the event.

Outcome of the AE will be recorded as defined in Table 4.

Table 4 - Adverse Event Outcome

1. Recovered/Resolved - One of the possible results of an adverse event outcome that indicates that the event has improved or recuperated. The subject recovered from the AE. Record the AE stop date.
2. Recovering/Resolving - One of the possible results of an adverse event outcome that indicates that the event is improving. No AE stop date should be recorded.
3. Not recovered/Not resolved/Ongoing - One of the possible results of an adverse event outcome that indicates that the event has not improved or recuperated. No AE stop date should be recorded.
4. Recovered/Resolved with sequelae - One of the possible results of an adverse event outcome where the subject recuperated but retained pathological conditions resulting from the prior disease or injury. Record the AE stop date. The AE stop date will represent the date the AE stabilized with no change in event outcome anticipated.

5. Continuing with Changed Intensity - One of the possible results of an adverse event outcome where the subject experiences a continuation of an AE but its severity is either increased or decreased compared to last report.
6. Fatal - The AE directly caused death. Record the date of death as the AE stop date.
0. Unknown - There is an inability to access the subject or the subject's records to determine the outcome (i.e., subject withdraws consent or is lost to follow-up). No AE stop date should be recorded.

6.1.2 Serious Adverse Events

An AE is considered "serious" if in the view of either the investigator or Sponsor, it meets one or more of the following criteria:

- Is fatal;
- Is life-threatening;
- Results in subject hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly/birth defect;
- Is an important medical event.

Important medical events are those that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE.

Since SAEs are critically important for the identification of significant safety problems, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or the investigator believes that an event is serious and related to IMP (i.e., assessed as possibly, probably, or definitely related), the event must be considered serious and evaluated by the Sponsor for expedited reporting.

Information about all SAEs will be collected and recorded on the Serious Adverse Event Report Form and must be reported to Contract Research Organization (CRO) Pharmacovigilance group within 24 hours of learning of its occurrence.

Events not to be reported as SAEs are hospitalizations for the following:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen;

- admission to a hospital or other institution for general care, not associated with any deterioration in condition;
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of SAE given above and not resulting in hospital admission.

Any SAE occurring after the moment of signing ICF and up until 4 weeks after the last dose of the study medication must be reported to the CRO's Pharmacovigilance Unit. SAEs occurring after the study termination must be reported only if considered IMP related as per investigator judgment.

Instructions about completing initial and follow-up SAE Report Forms and reporting to the CRO are given in Section 9.1.1 Serous Adverse Event Reporting.

6.1.3 Physical Examination

A complete physical examination that includes assessment of head (external), eyes, ears, nose and throat (HEENT), lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, central nervous system, ring size, and, where appropriate, other body systems, will be performed at Screening (V1a), V3 and V16 as indicated in the relevant table.

Physical examination will include height measurement at Screening and weight measurement at certain study visits. The study site must use calibrated equipment with subjects required to remove their shoes and heavy objects from their clothing prior to height and weight measurement, respectively.

At V4, V6, V7, V9, V10, V12, V13, V14 and V15 a symptom related physical examination (with weight measurement as appropriate) will be performed. Ring size should be measured at V14.

Any confirmed clinically significant physical examination abnormalities occurring after the moment of signing ICF are to be recorded as AEs.

6.1.4 Vital Signs

Vital signs (blood pressure at rest, pulse rate, respiratory rate and body temperature) will be assessed as per standard practice at relevant study visits as indicated in Table 1.

Blood pressure (resting) should be measured with calibrated digital equipment in the supine position after resting quietly for 5 minutes.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure and pulse rate measurements will be repeated at the investigator's discretion. Any confirmed clinically significant vital sign measurements occurring before signing the ICF are to be designated as medical history.

6.1.5 ECG Assessment

A standard 12-lead ECG will be performed in triplicate (approximately 1 minute apart) after the subject has rested quietly in the supine position for at least 10 minutes without significant stimulation (noise, TV, etc.) will be performed at V1a, V2, V3 (pre-dose), V4, V7, V10, V13, V14 and V16 only. When possible, the ECGs should be performed while fasting approximately 2 hours

after the study drug dosing. The ECG parameters that will be assessed include a summary of findings as well as measurement of the heart rate, QT, QTcF, and PR intervals, and QRS duration based on the ECG machine readings.

All ECG assessments will be initially assessed by the investigator for any findings that require immediate medical attention and will also be read by an ECG central reader. The clinical significance of any ECG findings will be determined by the investigator, including after the central reading result is available. However, only ECG results provided by the central reader will be recorded in the eCRF and clinical database. Any potentially significant outlier values should be confirmed by the central ECG reader. Any ECG measurement determined to be clinically significant (occurring after signing the ICF) will be noted as an AE on the appropriate eCRF page(s). Such abnormalities will be monitored until the end of the study or until resolution if considered related to the study drug.

6.1.6 Outpatient 24-hour Holter

An outpatient 24-hour Holter monitoring and recording will be conducted during the Screening Period. An adequate Holter recording should be confirmed by the central laboratory as soon as possible after completion, so that a repeat Holter monitor may be performed, if necessary, prior to Treatment Period.

6.1.7 Cardiovascular Safety Monitoring

Cardiology consultation should be obtained within 7 days for new clinically important symptoms or findings judged by the investigator reasonably likely to be of cardiac origin, e.g., evidence for new arrhythmia, significant chest discomfort/pain, presyncope or syncope.

Study drug must be stopped, and the medical monitor notified within 24 hours for any of the following:

- Based on the average of triplicate ECGs, QTcF >500 msec (or QTc >530 msec in subjects with a bundle branch block) repeated on a second set of ECGs at least 2 hours apart and confirmed by a stat central ECG reading;
- Any ventricular tachyarrhythmia associated with symptoms of hemodynamic response;
- Sustained ventricular tachycardia (lasting >30 sec) irrespective of symptoms;
- Torsades de pointes;
- Cardiac arrest;
- Pause >5 sec;
- Type 2 second degree block or third degree AV block;
- New occurrence of clinically significant, symptomatic bradycardia;
- An increase in QTcF >75 msec with an absolute QTcF <500msec (confirmed by the central ECG laboratory);
- Initiation of a concomitant medication during the Treatment Period which prolongs the QT interval (regardless of association with torsades de pointe). Medications associated with torsades de pointes (as listed in Appendix 2 - Medications Associated with Torsades

De Pointes) are exclusionary during the screening process and are not allowed as a concomitant medication at any time during the study (see Section 4.7.2);

- Any supraventricular tachyarrhythmia associated with symptoms of hemodynamic response.

The MM and investigator will determine the appropriateness of any further study drug dosing after stabilization of any of the above events.

Medications that are known to cause heart rate slowing (beta-blockers, verapamil, diltiazem, or ivabradine) may be started during the study if resting pulse is ≥60 bpm and if approved by the Medical Monitor. An unscheduled ECG should be performed approximately 5 days after starting the new medication to assess HR and QTcF.

6.1.8 Laboratory Assessments

All analyses must be done with the minimally required blood amount and the number of needle insertions should be minimized during the blood collection.

With the exception of the screening visit, V4, V7, V10, V13, and V15, all clinical laboratory assessments will be obtained from fasted subjects.

All laboratory samples will be shipped to Q^2 Solutions.

Laboratory management details are described in a Laboratory Manual.

After sampling, blood collection tubes will be labelled and handled as defined in the Laboratory Manual.

All results (except PK, GH, IGF-1 and [redacted]) will be reported to the investigator after completion of analyses.

All laboratory reports received must be reviewed, assessed for clinical significance, signed, and dated by the investigator or delegated sub-investigator. A legible copy of all reports must be filed in a subject medical record (source document) for that visit and the data recorded in the eCRF. Any laboratory test result (occurring after the moment of signing ICF) considered by the investigator to be clinically significant will be recorded as an AE and will be managed as described in section 6.1.1.

Hematology, $HbA1_C$

The complete blood count (CBC) with differentials will be evaluated as one of the safety parameters. The full panel of hematology analysis will comprise the following parameters: hemoglobin (Hgb), hematocrit (HCT), red blood cell (RBC) count, white blood cell (WBC) count with differential [neutrophils (Ne), eosinophils (Eo), basophils (Ba), monocytes (Mono) and lymphocytes (Lym)], and platelets (PLT), mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), will be evaluated at study visits, as indicated in the relevant table.

$HbA1_C$ will also be evaluated from this sample. $HbA1_c$ will be measured at selected visits as indicated in Table 1.

Serum chemistry

Blood collected for serum chemistry will be evaluated at study visits, as indicated in Table 1. The following parameters will be evaluated: total protein, urea, creatinine, uric acid, sodium, potassium, chloride, calcium, phosphate, magnesium, albumin, total bilirubin, direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), amylase, lipase and glucose. Fasting lipid panels (total cholesterol, LDL, HDL and triglycerides) will be measured at selected visits as indicated in Table 1.

Serum pregnancy test

Serum pregnancy test will be performed in women of childbearing potential at Screening only. Urine pregnancy tests will be performed thereafter as scheduled in Table 1.

Urine Analyses

The urinalysis profile will include the following: glucose, white blood cells (WBC), urine protein, bilirubin, nitrites, ketones, blood, pH, gravity and appearance. Urine samples will be collected and assessed by dipstick at all study visits as indicated in Table 1.

In addition, a urine pregnancy test will be performed in women of childbearing potential and will be performed at relevant study visits as indicated in Table 1.

Furthermore, a urine drug screen (for amphetamine, barbiturates, cocaine, methamphetamine, methadone, opiates, phencyclidine, and methylenedioxymethamphetamine) will be performed at Screening in all subjects.

Hormone levels

Thyroid hormone levels (fT3, fT4, TSH), thyroid antibody, cortisol, ACTH, LH, FSH and prolactin will be checked at Screening (V1b) and V14 as indicated in Table 1.

Serology Parameters

All subjects will be tested for HBV, HCV and HIV at Screening (V1a), as indicated in Table 1.

Genotype analysis

Blood sample for genotyping will be analyzed and will be collected for characterizing UGT1A1 genotype. Subjects may opt out of this genotype analysis.

IGF-1 levels and [redacted] levels (PD analysis)

Serum IGF-1 levels and [redacted] levels will be assessed throughout the study as safety and efficacy parameters at relevant time-points, as indicated in Table 1 and will be determined by immunoassay using the IDS-iSYS assay platform.

[redacted] levels will be measured for certain samples, i.e., only for *samples 1, 2, 4, 7, 10, 13, 14 and 16*.

GH levels (integrated)

Integrated is defined as three values taken at least 30 min apart over 2 hours. These samples will be collected as indicated in Table 1.

CRN00808 levels (PK analysis)

Blood samples to evaluate plasma concentrations of CRN00808 will be collected during the Treatment Period and during the Follow-up Period, as indicated in Table 1. Measurement of CRN00808 concentration will be done by a central bioanalytical laboratory using validated methods. Any remaining plasma may be used for metabolite profiling or measuring concentration of CRN00808 metabolites.

Residual octreotide/lanreotide/pasireotide plasma sample

Blood samples to evaluate plasma concentrations of octreotide, lanreotide, or pasireotide will be collected during the Screening and Treatment Period, as indicated in Table 1. Measurement of octreotide and lanreotide concentration will be done by a central bioanalytical laboratory using validated methods. Measurement of pasireotide concentration will be done, if necessary.

6.1.9 Gall bladder Ultrasound

A gall bladder ultrasound will be performed at Screening (completed by V2 if a recent documented ultrasound conducted within 3 months of V1a is not available) and V14 as indicated in Table 1.

It will be performed according to the study site procedures for the evaluation of presence or absence of lithiasis or sludge. The results will be recorded in the eCRF specific.

6.1.10 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging of the head with pituitary imaging will be performed at Screening. A recent documented scan conducted within 6 months of V1a is also acceptable to qualify a subject for the study.

If it is necessary to obtain an MRI during the Screening Period, it should be performed by the relevant department of the hospital or a private radiological practice, according to the usual practice. Management of subjects prior to and during the MRI should follow standard local procedures.

Pituitary CT scanning may serve as an alternative to MRI for subjects who are not eligible for MRI scanning.

6.1.11 Investigator Assessed Symptoms of Acromegaly

At V1a, the investigator will record specified acromegaly symptoms, including assessment of symptom intensity (mild, moderate or severe). At V1a only, there will also be an assessment of which symptom, if any, is most bothersome. These symptoms will be reassessed and monitored at all subsequent visits and occurrence of new symptoms or changes in symptom intensity compared to V1a assessment will be recorded as AEs as appropriate.

Acromegaly symptoms that will be assessed at the study entry and followed-up throughout the study include:

- Headache;
- Excessive sweating (hyperhidrosis);
- Swelling of extremities;
- Joint pain;
- Symptoms of sleep apnea;
- Fatigue;
- Paresthesia.

In case that any of these AEs are considered to represent a significant worsening of symptoms associated with acromegaly as judged by the investigator, the investigator will be responsible for reporting these AEs to the unblinded CRO designate within 24 hours in order to assess criteria for resumption of standard acromegaly treatment (see Section 3.1).

6.1.12 [redacted]

Subjects will complete [redacted] at home periodically throughout the study and results will be entered into the EDC. Subjects will complete [redacted] daily beginning the day after V1b through V3; daily beginning the day after V13 through V14; and daily beginning the day after V15 through V16.

[redacted] should be completed at home approximately the same time of day as consistently as possible. Site staff will review subject compliance with [redacted] completion at each study visit as indicated in Table 1. Responses to the [redacted] will not be reconciled with Adverse Event data.

[redacted]

6.1.13 [redacted]

[redacted] assessments will be performed at V3, V14 and V16. The questionnaires will be completed by the subject following standardized instructions at scheduled study visits and results recorded by site personnel in EDC. Quality of life questionnaires should be completed at the beginning of specified visits prior to other study procedures.

6.1.14 Patient Global Impression of Severity and Improvement

The Patient Global Impression of Severity (PGI-S) is a single question regarding overall current acromegaly symptom severity that will be completed by the subject at all study visits and results recorded by site personnel in the EDC. The Patient Global Impression of Improvement (PGI-I) is a single question regarding overall acromegaly symptom change compared to before study start that will be completed by the subject at visits designated in Table 1 and results recorded by site personnel in the EDC. PGI-S and PGI-I should be completed after Quality of Life questionnaires and before any other study procedures.

7 STATISTICAL ANALYSIS

7.1 Study Endpoints

EFFICACY ENDPOINTS

Primary endpoint:

The primary endpoint is the change from baseline (mean of Screening values) in IGF-1 level at W13.

Key Secondary endpoints:

- Proportion of subjects with the mean of their last two consecutive IGF-1 measurements ≤ULN;
- Proportion of subjects with the mean of their last two consecutive IGF-1 measurements ≤1.5×ULN;

Exploratory endpoints:

- Proportion of subjects who achieve serum GH <5.0 ng/mL at W13.
- Proportion of subjects who achieve serum GH <2.5 ng/mL at W13;
- Change from baseline in serum GH levels measured at W13;
- Change from baseline in serum [redacted] levels measured at W13;
- Increase in serum GH, IGF-1, and [redacted] levels 3+ weeks after withdrawal of CRN00808;
- Change from baseline in symptoms of acromegaly as measured by total [redacted] score at W13;
- Change from baseline in symptoms of acromegaly as measured by individual [redacted] score at W13;
- Change from baseline in [redacted] score at W13;
- Change from baseline in [redacted] at W13;
- Change from baseline in investigator assessed symptoms of acromegaly at W13;
- Change from baseline in PGI-S scores at W13;
- PGI-I scores at W13;
- Plasma concentrations of CRN00808.

SAFETY ENDPOINTS:

- Adverse events (AEs)/Treatment-emergent Adverse Events (TEAEs) throughout the study;
- Clinical laboratory tests (hematology, serum chemistry and urinalysis) at each post-baseline study visit;
- Vital signs at each post-baseline study visit;
- Physical examinations at each post-baseline study visit;
- 12-lead ECG at each post-baseline study visit;

- fT3, fT4, anti-thyroid antibody, TSH, cortisol, ACTH, LH, FSH and prolactin at each post-baseline study visit;
- Gall bladder ultrasound.

7.2 Statistical Methods and Analyses

7.2.1 Determination of Sample Size

Approximately 45 subjects are planned to be enrolled in the study. At least 30 subjects from Groups 1 and 2 will be enrolled, i.e., a cap of N=15 is set for the sum of the number of subjects in Group 3 to 5.

The primary objective of this study is to evaluate efficacy (IGF-1 levels) in subjects who are partial responders to somatostatin analogue based treatment regimens. As such, the sample size is chosen to provide sufficient clinical experience to evaluate IGF-1 changes descriptively and is not formally powered for hypothesis testing. Summary statistics for the primary endpoint will be provided.

7.2.2 Analysis Datasets

Safety Analysis Set comprises all subjects who received at least one dose of the study medication. The Safety Analysis Set will be used for all safety analyses and for some of the secondary efficacy endpoints.

Efficacy Analysis Set comprises all subjects from Groups 1 and 2 who received at least one dose of the study medication. The Efficacy Analysis Set will be used for the evaluation of the primary efficacy endpoint and for some of the secondary efficacy endpoints.

Per Protocol Analysis Set (PP) comprises all subjects from the Efficacy Analysis Set having no major protocol deviation affecting treatment efficacy. The PP analysis set will be used for supportive efficacy analyses.

7.2.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized in a descriptive manner.

7.2.4 Treatment Assignment and Study Medication

Not applicable. As this is an open label study, it is not deemed feasible to employ blinding methods among the five groups. After the initial starting dose, further dose increases/decreases are blinded to the investigator and subject.

7.2.5 Efficacy Analysis

7.2.5.1 Analysis of Primary Endpoint

For the primary endpoint, change from baseline (mean of Screening values) in IGF-1 level at W13, descriptive statistics (n, mean, SD, 90% CI of mean, min, max, median) will be presented on the Efficacy Analysis Set and on the PP Analysis Set.

7.2.5.2 Analysis of Secondary and Exploratory Endpoints

All quantitative endpoints will be summarized using descriptive statistics, as described for the primary endpoint. Results will be provided for all groups combined, for groups 1 and 2 combined (the Efficacy Analysis Set), and for each of the five groups separately. All proportional endpoints will be similarly summarized using counts and percentages.

7.2.6 Safety Analysis

Safety endpoints will be summarized with descriptive statistics and shift tables where applicable.

7.2.7 Interim Analysis

No interim analysis is planned.

8 DATA MANAGEMENT

8.1 Data Handling

Data will be collected by means of electronic Case Report Forms (eCRFs). The eCRF must be kept current to reflect subject status during the course of the study. A subject identification number will be used to identify the subject. Completion instructions will be provided in the eCRF Completion Guidelines document or as prompts and short instruction on the eCRF pages.

The study will use an Electronic Data Capture (EDC) system to collect the clinical trial data at the investigational sites. The system complies with 21 CFR Part 11 and ICH E6 Good Clinical Practice. Queries are generally sent to the investigational site using an electronic data query system which provides an automatic audit trail of the corrections made by designated investigator staff. All changes to the data have an electronic audit trail, in accordance with 21 CFR 11.10(e). Electronic signatures will be used in conformance with 21 CFR Part 11.

Source documents are to be retained to enable a reconstruction and evaluation of the trial. No original observations will be entered directly into the computerized system without source documentation.

Access to the EDC system is controlled with user ID and password and can only be granted to appropriately trained users. Different types of users will have different privileges assigned in the EDC system. A user access list is maintained throughout the study.

The Investigator will receive a CD/DVD or USB pen drive of the subject data for archiving at the investigational site following the database lock and before the study site close out visit.

8.1.1 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

8.1.2 Coding Dictionaries

Concomitant medications entered into the database will be coded using the most recent version of the World Health Organization (WHO) Drug Dictionary which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases, medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 21.0 or higher.

8.2 Data Management and Quality Control

Database quality will be assessed early in the study conduct. Data queries will be quantified and reviewed by site and by data type and program to highlight any data issues which can be addressed through additional training or enhancements to the data validation programs.

A formal quality control (QC) will be conducted prior to database lock.

Any required changes to the database design and programming will be managed through a detailed change control process.

8.3 Database lock

The database will be locked prior to unblinding.

Details of database lock will be documented in appropriate Data Management Plan.

9 STUDY MANAGEMENT/PROCEDURES AND INSTRUCTIONS

9.1 Safety Related Procedures

9.1.1 Rapid Notification on Serious Adverse Events

Any SAE occurring after the moment of signing ICF and up until 4 weeks after the last dose of study medication must be reported to the CRO's Pharmacovigilance Unit. SAEs occurring after the study termination must be reported only if considered IMP related as per investigator judgment.

Any such SAE due to any cause, whether or not related to the IMP, must be reported on the SAE reporting form within 24 hours of occurrence or when the investigator becomes aware of the event. Properly completed SAE reporting form should be sent via email. However, notification can also be made using the telephone line for the CRO's Pharmacovigilance Unit:

CRO Pharmacovigilance Group e-mail: [redacted]

CRO Pharmacovigilance Group Telephone Number: [redacted]

If the investigator contacts the CRO's Pharmacovigilance Unit by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae (if any) in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be provided whether or not the investigator considers the event to be related to the IMP.

Appropriate measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The investigator must report all available additional follow-up information to the CRO's Pharmacovigilance Unit within 24 hours. All SAEs will be followed until the investigator and Sponsor agree the event is satisfactorily resolved.

SUSARs (i.e., unexpected SAEs considered drug related as assessed by the Investigator/Sponsor/authorized person) will qualify for expedited reporting and cross reporting to the IRB/EC, Competent Authorities, and participating Investigators.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed until its resolution or stabilization.

9.1.2 Rapid Notification on Pregnancies

Female subjects of childbearing potential must have a negative pregnancy test at Screening. Following administration of the IMP, any known cases of pregnancy in female subjects will be reported by telephone (optional) and by emailing a completed Pregnancy Report to the Sponsor/CRO's Pharmacovigilance Unit within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE. However, the investigator will follow-up with the

subject or female partner of the male subject (after obtaining informed consent, as appropriate) until completion of the pregnancy and must determine the outcome of the pregnancy in the shortest possible time. The Investigator should notify the Sponsor/CRO's Pharmacovigilance Unit of the pregnancy outcome by submitting a follow-up Pregnancy Report. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by telephone and by e-mailing a completed SAE form to the Sponsor/CRO's Pharmacovigilance Unit within 24 hours of knowledge of the event.

9.1.3 Overdose

The Investigator must notify the CRO's Pharmacovigilance Unit of any occurrence of overdose with IMP by telephone (optional) and by emailing a completed "*Overdose Notification Form"* within 24 hours.

Overdose will not be automatically recorded as AE. However, any undesirable medical occurrence resulting from an accidental overdose is an AE and should be recorded and reported on the appropriate AE eCRF. Since accidental overdoses of the study medications could have serious clinical consequences and/or represent compliance issue, they should be reported to and evaluated by the Sponsor. The investigator should record the event in the source document and should monitor the subject.

9.1.4 Emergency Procedure for Un-blinding

The investigator should contact the CRO's Pharmacovigilance Unit to request the unblinding of the study drug dose during the Treatment Period.

9.1.5 Central IGF-1 Reader

Investigators and subjects will be blinded to IGF-1 results during the study. The unblinded central IGF-1 reader will determine if protocol specified criteria are met for dose up-titrations based on IGF-1 results. An up-titration also requires the investigator's assessment of tolerability of the study drug. An unblinded CRO delegate will ensure that appropriate blinded blister cards are assigned based on information from the central reader and from the investigator. All appropriate measures will be taken to keep the blinded study team members and investigational site personnel blinded to subjects' study drug dose throughout the study. Further details on responsibilities and procedures will be described in a separate document (Central IGF-1 Reader Procedures Manual).

9.2 Regulatory Issues, Ethics and Good Clinical Practice

9.2.1 Regulatory Guidelines and Ethical Considerations

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 54, 56, and 312 of Title 21 of the Code of Federal Regulations (CFR), in compliance with GCP guidelines, and as per all applicable local regulatory guidelines and Directive of the European Parliament, guidelines set

out in Volume 10 of the publications "The rules governing medicinal products in the European Union" and other applicable European Medicines Agency (EMA) regulations.

Declaration of Helsinki and amendments can be accessed via the website of the World Medical Association at https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

9.2.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Approval is required for the Clinical Study Protocol, Investigational Drug Brochure, protocol amendments, ICFs, and subject information sheets.

9.2.3 Informed Consent

For each study subject, written informed consent will be obtained prior to any protocol-related activities. It must be signed and dated personally by the subject and by the Investigator and/or the study team member designated by the Investigator to conduct the informed consent procedure.

As part of this procedure, the Principal Investigator or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the study is aware of the potential risks, inconveniences, or adverse effects that may occur. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and International Council for Harmonization (ICH) guidelines. The PI will provide the Sponsor or its representative with a copy of the IRB/IEC approved ICF prior to the start of the study.

9.2.4 Sponsor

The Sponsor or its designee (e.g., CRO) will provide protocol training to the site study personnel, as appropriate. Clinical monitors will conduct site visits, as needed, to ensure the site procedures are being carried out in accordance with the Clinical Study Protocol and GCP. Throughout the study period, the clinical monitor will be available to address any issues that may arise. This availability includes access by phone and e-mail.

Injury in subjects possibly arising from participating in this trial is covered by the liability insurance of the Investigator or Sponsor. This insurance provides coverage for damage to the subjects through injury or death caused by the trial.

9.2.5 Principal Investigator

The Principal Investigator, together with any designated co-investigators, has the overall responsibility for the conduct and compliance of this clinical trial according to this Clinical Study Protocol and GCP.

Investigators and other key personnel shall provide curriculum vitae or equivalent, that will confirm their suitability for the clinical study. All investigators and key personnel should be listed together with their responsibilities in the study on a signature and delegation log.

It is the responsibility of the investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge of and training in all procedures to be followed.

Language: All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

9.3 Administrative Procedures

9.3.1 Protocol Amendment and Protocol Deviations

Protocol Amendment

Amendments to the Clinical Study Protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IRB/IEC and Regulatory Authorities for information only. The Sponsor (or designee) will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IRBs/IECs for approval.

Protocol Deviations

Should protocol deviations that affect subject safety occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations will be included in the Clinical Study Report (CSR). Reporting of the protocol deviations to the IRB/IEC and in accordance with applicable Regulatory Authority mandates will be performed.

No prospective entry criteria protocol deviations are allowed; all subjects must meet all eligibility criteria in order to participate in the study. Protocol waivers for eligibility will not be granted by the Sponsor under any circumstances. If during the course of a subject's post-enrolment participation in the trial it is discovered that the subject did not meet all eligibility criteria, the subject will be discontinued.

9.3.2 Monitoring Procedures

The study will be monitored to ensure that it is conducted and documented properly according to the Clinical Study Protocol, GCP, and all applicable regulatory requirements.

Before the study start, at a site initiation visit or at an investigator's meeting, a Sponsor representative will review the protocol and the eCRF with the investigators and their staff.

During the study, on-site monitoring visits will be made at appropriate times. Clinical monitors will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRF, the adherence to the Clinical Study Protocol and to GCP, the progress of enrollment, and to ensure that IMP is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the clinical monitor during these visits.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Full verification for the presence of informed consent,

adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables will be checked. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

9.3.3 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application in an ICH region or as per local requirements, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information. The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with Directive 95/46/EC: Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data and in a form satisfactory to the Sponsor.

9.3.4 Quality Control and Quality Assurance

The study will be conducted according to GCP as outlined by ICH topic E6, step 5 guidelines. The CRO maintains a quality assurance system with written SOPs to ensure that clinical trials are conducted, and data are generated, documented and reported in compliance with the Clinical Study Protocol, GCP and applicable regulatory requirements.

The Sponsor or its designee will perform the quality assurance and quality control activities of this study. However, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the Clinical Study Protocol, Standard Operating Procedures (SOP), GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at the study sites and during data management to assure that safety and efficacy data are adequate and well documented.

Investigators/Institution will permit trial related audits, IRB/IEC review, and regulatory inspections, providing direct access to source data/documents.

9.3.5 Financing and Insurance

Prior to the study commencing, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

9.3.6 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this Clinical Study Protocol, subject to the terms of any such agreement. To facilitate such ownership, investigators will be required to assign all such inventions directly to the Sponsor as will be set forth in the clinical study agreement.

10 REFERENCES

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Appendix 1 - World Medical Association Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, Sponsor, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.
    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally

authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in bio banks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, Sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, Sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding,

institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2 - Medications Associated with Torsades De Pointes

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Aclarubicin (only on non-US market)	Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Anti-cancer	Cancer
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic	Arrhythmia
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox	Anti-cancer	Cancer (leukemia)
Astemizole (removed from market)	Hismanal	Antihistamine	Allergic rhinitis
Azithromycin	Zithromax, Zmax	Antibiotic	Bacterial infection
Bepridil (removed from market)	Vascor	Antianginal	Angina Pectoris (heart pain)
Chloroquine	Aralen	Antimalarial	Malaria
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic/Antiemetic	Schizophrenia, nausea, many others
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic	Bacterial infection
Cisapride (removed from market)	Propulsid	GI stimulant	Increase GI motility
Citalopram	Celexa, Cipramil	Antidepressant, SSRI	Depression
Clarithromycin	Biaxin, Prevpac	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Norpace	Antiarrhythmic	Arrhythmia
Dofetilide	Tikosyn	Antiarrhythmic	Arrhythmia
Domperidone (only on non-US market)	Motilium, Motillium, Motinorm Costi, Nomit	Antiemetic	Nausea, vomiting
Donepezil	Aricept	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Dronedarone	Multaq	Antiarrhythmic	Arrhythmia
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic/Antiemetic	Anesthesia (adjunct), nausea

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic	Bacterial infection, increase GI motility
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E (India), Exodus (Brazil), Esto (Israel), Seroplex, Elicea, Lexamil, Lexam, Entact (Greece), Losita (Bangladesh), Reposil (Chile), Animaxen (Colombia), Esitalo (Australia), Lexamil (South Africa)	Antidepressant, SSRI	Depression (major), anxiety disorders
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic	Arrhythmia
Fluconazole	Diflucan, Trican	Antifungal	Fungal infection
Gatifloxacin (removed from market)	Tequin	Antibiotic	Bacterial infection
Grepafloxacin (Removed from Market)	Raxar	Antibiotic	Bacterial infection
Halofantrine (only on non-US market)	Halfan	Antimalarial	Malaria
Haloperidol	Haldol (US & UK), Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol (Germany), Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic	Schizophrenia, agitation
Ibogaine (only on non-US market)	None	Psychedelic	Narcotic addiction, unproven
Ibutilide	Corvert	Antiarrhythmic	Arrhythmia
Levofloxacin	Levaquin, Tavanic	Antibiotic	Bacterial infection

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Levomepromazine (methotrimeprazine) (only on non-US market)	Nosinan, Nozinan, Levoprome	Antipsychotic	Schizophrenia
Levomethadyl acetate (removed from market)	Orlaam	Opiate	Narcotic dependence
Levosulpiride (only on non-US market)	Lesuride, Levazeo, Enliva (with rabeprazole)	Antipsychotic	Schizophrenia
Mesoridazine (removed from market)	Serentil	Antipsychotic	Schizophrenia
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opiate	Narcotic dependence, pain
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic	Bacterial infection
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic	Nausea, vomiting
Oxaliplatin	Eloxatin	Anti-cancer	Cancer
Papaverine HCl (Intra-coronary)	none	Vasodilator, Coronary	Diagnostic adjunct
Pentamidine	Pentam	Antifungal	Fungal infection (Pneumocystis pneumonia)
Pimozide	Orap	Antipsychotic	Tourette's Disorder
Probucol (removed from market)	Lorelco	Antilipemic	Hypercholesterolemia
Procainamide	Pronestyl, Procan	Antiarrhythmic	Arrhythmia
Propofol	Diprivan, Propoven	Anesthetic, general	Anesthesia
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic	Arrhythmia
Roxithromycin (only on non-US market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Antibiotic	Bacterial infection
Sevoflurane	Ultane, Sojourn	Anesthetic, general	Anesthesia
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic	Arrhythmia

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Sparfloxacin (removed from market)	Zagam	Antibiotic	Bacterial infection
Sulpiride (only on non-US market)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical	Schizophrenia
Sultopride (only on non-US market)	Barnetil, Barnotil, Topral	Antipsychotic, atypical	Schizophrenia
Terfenadine (removed from market)	Seldane	Antihistamine	Allergic rhinitis
Terlipressin (only on non-US market)	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss and others	Vasoconstrictor	Septic shock
Terodiline (only on non-US market)	Micturin, Mictrol (not bethanechol)	Muscle relaxant	Bladder spasm
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic	Schizophrenia
Vandetanib	Caprelsa	Anti-cancer	Cancer (thyroid)