An Open Label, Randomized, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of IONIS-GHR-LRx, an Antisense Inhibitor of the Growth Hormone Receptor, Administered Monthly as Monotherapy in Patients With Acromegaly

NCT04522180

30 August 2022

ionispharma.com

2855 Gazelle Court
Carlsbad, CA 92010

(760) 931-9200

IONIS PHARMACEUTICALS, INC.

ISIS 766720-CS5

An Open Label, Randomized, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor, Administered Monthly as Monotherapy in Patients with Acromegaly

Protocol Amendment 3 – 13 December 2021

EudraCT No: 2020-000675-20

Trial Sponsor

Ionis Pharmaceuticals
2855 Gazelle Court
Carlsbad, CA 92010
Phone: 760 931 9200
Fax: 760 603 3564

[redacted]

ISIS 766720-CS5

Amendment 3

EudraCT No: 2020-000675-20

Clinical Phase: 2

An Open Label, Randomized, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor, Administered Monthly as Monotherapy in Patients with Acromegaly

Protocol History:

Original Protocol:	25 February 2020
Amendment 1:	31 July 2020
Amendment 2:	7 July 2021

Sponsor
Ionis Pharmaceuticals, Inc.
Carlsbad, CA 92010

[redacted]

Confidentiality Statement

Protocol Signature Page

Protocol Number:	ISIS 766720-CS5
Protocol Title:	An Open Label, Randomized, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor, Administered Monthly as Monotherapy in Patients with Acromegaly
Amendment:	Amendment 3
Date:	13 December 2021

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "An Open Label, Randomized, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor, Administered Monthly as Monotherapy in Patients with Acromegaly" dated 13 December 2021, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL AMENDMENT

Protocol Number:	ISIS 766720-CS5
Protocol Title:	An Open Label, Randomized, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor, Administered Monthly as Monotherapy in Patients with Acromegaly
Amendment Number:	3
Amendment Date:	13 December 2021

The primary purpose of this amendment is to update the patient randomization and clarify enrollment of treatment dose groups. Because some participating countries did not have regulatory approval for all dose levels, the Sponsor has decided to provide all sites the opportunity to enroll patients in their region at an approved dose level. To facilitate this, patients will continue to be randomized through the IVR system; however, it may not necessarily be equally in a 1:1:1 manner. Additionally, the Sponsor decided to assess the safety and efficacy of the higher dose levels prior to deciding to conduct the 80-mg treatment group.

Additionally, Protocol Section 8.5.3 was updated to provide clarification to contact the Sponsor Medical Monitor prior to any modifications in safety monitoring.

These updates do not change the safety and efficacy objectives of the trial.

Also, administrative clarifications and corrections for typographical errors have been made throughout the protocol to improve the overall clarity of the original protocol; however, these changes do not impact subject safety, exposure, or the overall study design.

The following modifications to Protocol ISIS 766720-CS5 have been made. Changes to the protocol language are **bolded** and **underlined**. The table below provides a list of changes to the protocol:

Protocol Section	Description of Change
Protocol Synopsis: Number of Patients	Approximately 40 patients are planned to be randomized in the study. Thirty-six (36) patients (12 in each treatment group) in the per protocol set (PPS) are needed to complete the Treatment Period and the primary efficacy endpoint. ~~Patients will be randomized equally (1:1:1) to 1 of the 3 treatment groups (80 mg, 120 mg, 160 mg)~~. **Patients will be enrolled to either the 120 mg or the 160 mg groups initially. After review of the safety and efficacy data in approximately 50% of the patients, the 80 mg group may be enrolled. If the 80 mg treatment group is not conducted, approximately 30 patients will be randomized.**

Protocol Section	**Description of Change**
Protocol Synopsis: Statistical Considerations	Eligible patients will be stratified based on screening serum IGF-1 level (> 2.5× ULN vs. ≤ 2.5 × ULN age and sex adjusted by the central lab) and then patients will be randomized to ~~1 of 3~~ **one of the** treatment groups (ISIS 766720 80 mg, 120 mg or 160 mg). ~~in a 1:1:1 ratio.~~
Protocol Section 3.3 Number of Patients	Thirty-six (36) patients (12 in each treatment group) in the per protocol set (PPS) are needed to complete the Treatment Period and the primary efficacy endpoint. **If the 80 mg treatment group is not conducted, approximately 30 patients will be randomized.**
Protocol Section 4.2 Randomization	Eligible patients will be stratified based on screening IGF-1 levels (≤ 2.5 × ULN or > 2.5 × ULN age and sex adjusted by central lab) and then patients will be randomized ~~equally (1:1:1)~~ to ~~1 of the 3~~ **one of the** ISIS 766720 dose treatment groups (80 mg, 120 mg, 160 mg). The Sponsor or Designee will prepare the randomization list. **Patients will be enrolled to either the 120 mg or the 160 mg groups initially. After review of the safety and efficacy data in approximately 50% of the patients, the 80 mg group may be enrolled.**
Protocol Section 8.5.3	Safety Monitoring for Minor Bleeding Events Minor bleeding events are those that do not fulfill the criteria for major bleeding (MB) or clinically relevant, non-major bleeding events (which are defined in Section 8.6.3). If a minor bleeding event occurs, additional testing of coagulation parameters (activated partial thromboplastin time [aPTT], prothrombin time [PT], INR) and platelet count ~~should~~ **may** be performed **after consultation with the Sponsor Medical Monitor or Designee.**
Protocol Section 9.3.3 Serious Adverse Event	The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; ~~OR Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials;~~ the event itself may be of relatively minor medical significance [such as severe headache without any further findings]).
Protocol Section 10.2 Sample Size Considerations	Approximately 40 patients are planned to be randomized in the study. **If the 80 mg treatment group is not conducted, approximately 30 patients will be randomized.**

PROTOCOL SYNOPSIS

Protocol Title	An Open Label Randomized, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor, Administered Monthly as Monotherapy in Patients with Acromegaly
Study Phase	2
Indication	Acromegaly
Primary Objectives	To evaluate the safety and tolerability of ISIS 766720 subcutaneous (SC) injection as a monotherapy in patients with acromegaly. To evaluate the efficacy of ISIS 766720 SC injection on serum insulin-like growth factor-1 (IGF-1) as a monotherapy in patients with acromegaly.
Secondary Objective	To evaluate the effect of ISIS 766720 SC to normalize serum IGF-1 levels.
[redacted]	
Study Design	This will be a Phase 2, randomized, open label multi-center study.
Number of Patients	Approximately 40 patients are planned to be randomized in the study. Thirty-six (36) patients (12 in each treatment group) in the per protocol set (PPS) are needed to complete the Treatment Period and the primary efficacy endpoint. [redacted]

PROTOCOL SYNOPSIS CONTINUED

Study Population	**Inclusion Criteria** 1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements 2. Males or females with a documented diagnosis of Acromegaly* who are 18 to 75 years old (inclusive) at the time of informed consent * Defined as a previous diagnosis of GH-secreting adenoma by surgical pathology; or the presence of a pituitary adenoma identified on magnetic resonance imaging (MRI) or computed tomography (CT) Scan (if MRI is contraindicated) and serum IGF-1 levels above the upper limit of normal (ULN) for age and sex at time of diagnosis (serum IGF-1 level and imaging at diagnosis will be collected in the case report forms [CRF]) 3. Have had pituitary surgery (e.g. transsphenoidal) unless there was a contraindication to surgery **and** are either acromegaly medical treatment naïve, or who had not taken any other acromegaly medications prior to the screening visit as outlined below: bromocriptine: 2 weeks cabergoline: 4 weeks quinagolide: 4 weeks octreotide daily injection (SC) or oral formulation: 4 weeks pegvisomant: 4 weeks octreotide LAR: 3 months pasireotide LAR: 4 months lanreotide (all formulations): 3 months 4. At Screening, serum IGF-1 (performed at central lab) between 1.3 to 5 × ULN, inclusive, adjusted for age and sex. IGF-1 can be repeated once and averaged to determine eligibility if the initial result is between 1.1–1.3 × ULN, or between 5-5.3 = × ULN 5. Females must be non-pregnant and non-lactating, and either: a. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) b. post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone (FSH) levels in the postmenopausal range for the laboratory involved) c. abstinent (defined in Section 6.3.1) or

PROTOCOL SYNOPSIS CONTINUED

Study Population Continued	**Inclusion Criteria Continued** d. Women of childbearing potential (WOCBP) should agree to taking all precaution to avoid pregnancy during the Trial Period (including Post-Treatment), including agreeing to receive pregnancy testing before each monthly dose, using 1 highly effective method of birth control (Section 6.3.1) from the time of signing the informed consent form (ICF) until 14 weeks after the last dose of ISIS 766720 administration Males must be either: e. surgically sterile f. abstinent (defined in Section 6.3.1) or g. if engaged in sexual relations with a female of child-bearing potential, the patient must be using a highly effective contraceptive method (refer to Section 6.3.1) from the time of signing the ICF until 14 weeks after the last dose of ISIS 766720 6. Willing to refrain from strenuous exercise/activity (for example heavy lifting, weight training, intense aerobics classes etc.) for at least 24 hours prior to study visits 7. Willing to refrain from alcohol or tobacco use for 8 hours prior to study visits **Exclusion Criteria** 1. Clinically significant (CS) abnormalities in medical history according to Investigator judgement (e.g., previous acute coronary syndrome within 6 months of Screening, major non-pituitary surgery within 2 months of Screening) or from Screening physical examination (PE) 2. Patients who received surgery for pituitary adenoma within the last 3 months before the trial, and/or planning to receive surgery during the trial 3. Patients who received radiotherapy for pituitary adenoma within the last 2 years before the trial, and/or planning to receive radiotherapy during the trial 4. Patients with a pituitary tumor that, per Investigator judgment, is worsening (e.g., either growing, or at risk of compressing or abutting the optic chiasm or other vital structures) as assessed by pituitary/sellar MRI protocol at Screening or within 3 months of Screening. CT scan is allowed if MRI is contraindicated. 5. Evidence of decompensated cardiac function per medical judgement and/or New York Heart Association (NYHA) Class 3 or 4

PROTOCOL SYNOPSIS CONTINUED

Study Population Continued	**Exclusion Criteria Continued** 6. Clinical evidence of symptomatic hyperprolactinemia that would necessitate treatment 7. Symptomatic cholelithiasis, and/or choledocholithiasis 8. Intentionally left blank 9. Patient with history of hypoglycemia unawareness (who have had > 3 severe episodes in the past 6 months) or documented reactive hypoglycemia 10. Screening laboratory results as follows, or any other CS abnormalities in Screening laboratory values that would render a patient unsuitable for inclusion (abnormalities may be retested for eligibility purposes) a. UPCR ≥ 500 mg/g. In the event of urine protein/creatinine ratio (UPCR) above this threshold eligibility may be confirmed by a quantitative total urine protein measurement of < 1000 mg/24 hr b. Positive test (including trace) for blood on urinalysis. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field c. alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 × ULN; alkaline phosphatase (ALP) > 3 × ULN; Total bilirubin ≥ 1.5 × ULN. Patients with Gilbert's syndrome may have total bilirubin ≥ 1.5 × ULN if only the indirect bilirubin is elevated > ULN and the ALT/AST is not greater than the ULN. d. eGFR < 45 mL/min/1.73 m^2 as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) equation for creatinine clearance OR serum creatinine > 1.8 mg/dL in males and > 1.5 mg/dL in females e. Platelet count < 125,000 mm^3 f. Abnormal thyroid function tests must be discussed with the Sponsor Medical Monitor or Designee g. HbA1c > 10% h. Abnormal morning cortisol test demonstrating symptomatic adrenal insufficiency based on investigator judgement 11. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1 12. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator

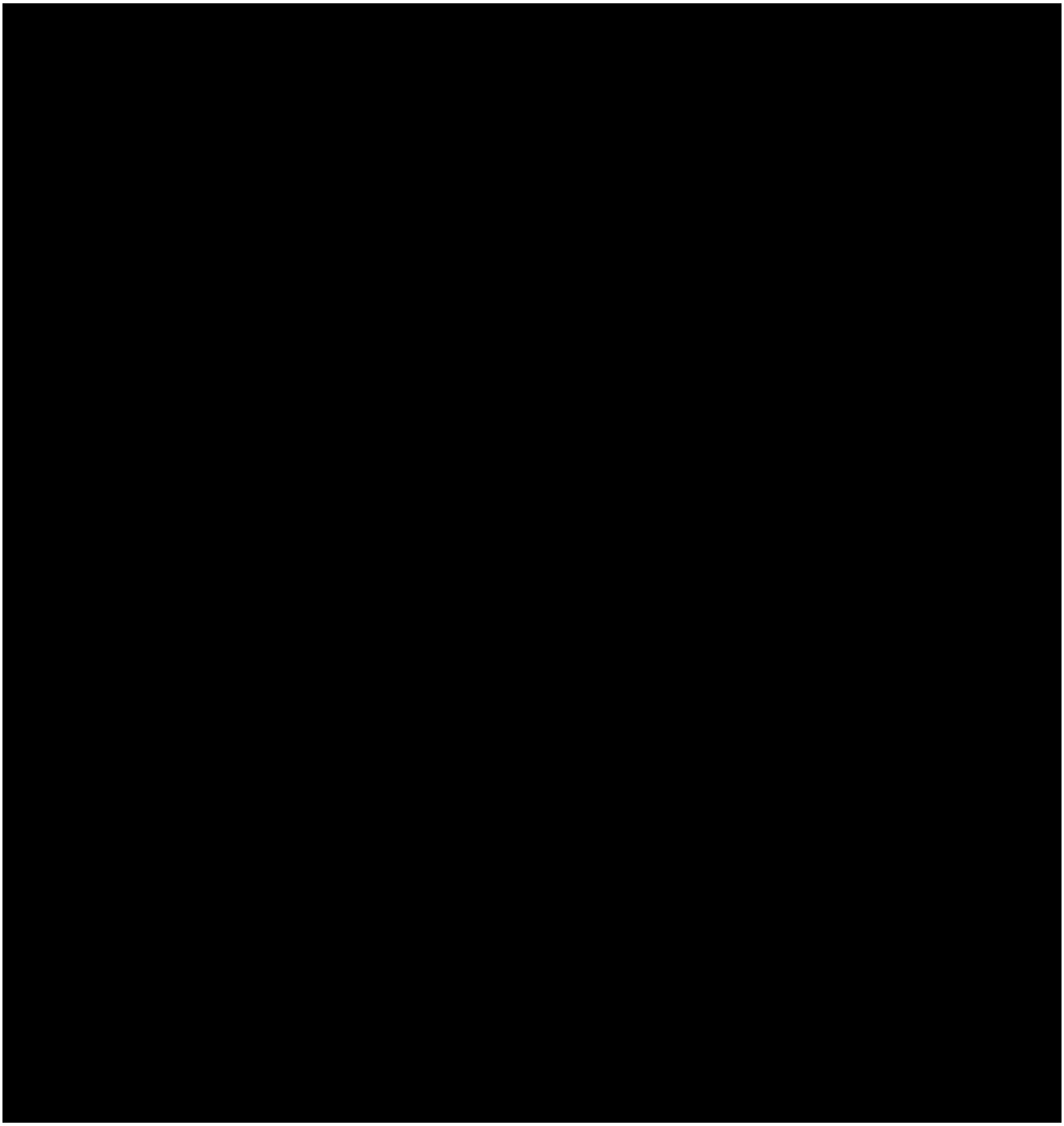
PROTOCOL SYNOPSIS CONTINUED

Study Population Continued	**Exclusion Criteria Continued**
	13. Active infection with human immunodeficiency virus (HIV), hepatitis C (HCV) or hepatitis B (HBV) diagnosed by initial serology testing and confirmed with RNA testing, or prior treatment for HCV. Patients at Screening who test positive by serology, but negative by RNA may be allowed in consultation with the Sponsor Medical Monitor or Designee 14. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin, carcinoma *in situ* of the cervix, follicular Stage 1 or papillary thyroid cancer that has been successfully treated; patients that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor or Designee 15. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer 16. Treatment with any non-ION- or ISIS-oligonucleotide (including small interfering ribonucleic acid [siRNA]) at any time or prior treatment with an ION- or ISIS-oligonucleotide within 9 months of Screening. Patients that have previously received only a single-dose of an ION- or ISIS-oligonucleotide as part of a clinical study may be included as long as duration ≥ 4 months has elapsed since dosing. This exclusion does not apply to vaccines (neither mRNA nor viral vector vaccines) 17. History of bleeding diathesis or coagulopathy 18. Recent history of, or current drug or alcohol abuse that could affect study compliance per Investigator judgment 19. Patients may not have chronic systemic use of weight loss medications (except GLP-1 agonist or SGLT2 inhibitors) or participate in weight loss programs within 2 months before Screening. Patients taking GLP-1 agonist or SGLT2 inhibitors indicated for weight loss maybe allowed with prior consultation with the Sponsor Medical Monitor or Designee 20. Patients on anti-diabetes medications must be on a stable dose and regimen for ≥ 3 months prior to Screening. Patients taking insulin can be allowed with prior consultation with the Sponsor Medical Monitor or Designee 21. Patients on estrogen containing medications must be on a stable dose and regimen for ≥ 3 months prior to Screening

PROTCOL SYNOPSIS CONTINUED

Study Population Continued	**Exclusion Criteria Continued** 22. Patients on glucocorticoid replacement used for adrenal insufficiency must be on a stable dose and regimen (increases used to prevent adrenal crisis is permitted) for ≥ 3 months prior to Screening 23. Use of oral anticoagulants, unless the dose has been stable for 4 weeks prior to the first dose of ISIS 766720 and regular clinical monitoring is performed during the trial 24. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening and during the trial 25. Have any other conditions, which, in the opinion of the Investigator and Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the Study
[redacted]	[redacted]
	All ISIS 766720 injections will be SC administered in the clinic during the first 17 weeks of the Treatment Period. Home health is an option at select visits.

PROTCOL SYNOPSIS CONTINUED



PROTCOL SYNOPSIS CONTINUED

Study Visit Schedule and Procedures	Detailed information regarding the study procedures is outlined in Section 6 of protocol. The study for an individual patient will generally consist of the following periods: • A ≤ 6-week Screening Assessment Period • A 73-week Treatment Period: ISIS 766720 will be administered as a once monthly SC injection (except during Month 1 where a booster dose is administered on Day 15). The primary endpoint will be evaluated at 6 months (Week 27) • A 14-week Post-Treatment Evaluation Period Laboratory and other study procedures will be performed to assess eligibility during the Screening Periods. In the Treatment Period patients will be randomized to a treatment group. Safety and tolerability will be assessed biweekly in the first 17 weeks and monthly after Week 17. A primary endpoint visit will occur at Week 27 (6 months). Efficacy, exploratory endpoints and plasma PK assessments will be conducted periodically during the Treatment Period. During the Post-Treatment Period, safety, exploratory and PK will be assessed for 14 weeks. The 2-hour OGTT and GH response assessments will be performed (3×) during the study (see Section 6.2.2 for details). An MRI (3×) and Echocardiogram (2×) will be done. See Appendix A. Assessment of acromegaly clinical symptoms, patient reported outcome, and ring size measurement will be monitored during the Treatment Period and the Post-Treatment Period. All safety data including adverse events (AEs) and concomitant medications will be reviewed by the Sponsor's Medical Monitor or Designee on an ongoing basis throughout the trial. Dose adjustments may be allowed after 17 weeks of treatment and only after consultation with Sponsor Medical Monitor (or Designee). If initiation of other acromegaly medication(s) is clinically indicated, according to the Investigator judgement, the patient will discontinue ISIS 766720 and enter the Post-Treatment Period. In order to allow the drug to reach therapeutic steady-state concentrations, it is recommended to wait until after Week 17 before initiating other acromegaly medications. All patients will complete the 14-week Post-Treatment Period after their last dose.
Primary Endpoint	The primary efficacy endpoint is the percent change in IGF-1 from Baseline to Week 27.

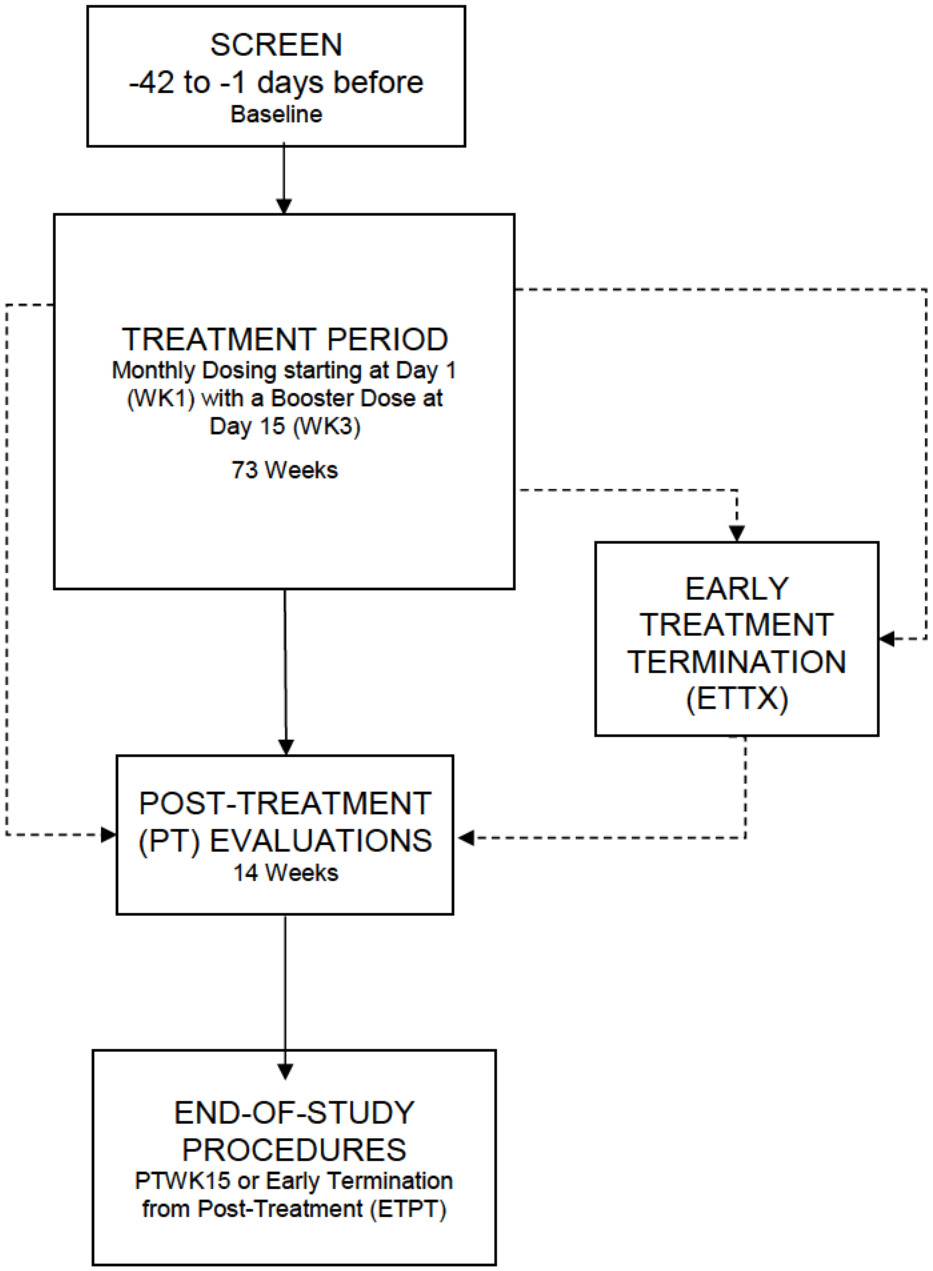
PROTCOL SYNOPSIS CONTINUED

Secondary Endpoints	The secondary efficacy endpoints include: • Patients who achieve normalized IGF-1 levels to within 1.2 times gender and age limits at Day 183 (Week 27) • Patients who achieve normalized IGF-1 levels to within 1.0 times gender and age limits at Day 183 (Week 27) • Change from Baseline in serum IGF-1 over time • Percent change from Baseline in serum IGF-1 over time
[redacted]	[redacted]
Safety Endpoints	The safety endpoints include incidence and severity of treatment-emergent adverse events (TEAE), use of concomitant medications, results of laboratory assessments, electrocardiogram (ECG), and vital signs.

PROTCOL SYNOPSIS CONTINUED

Statistical Considerations	[redacted] An interim analysis may be conducted when approximately 50% of patients complete the primary efficacy assessment.
Sponsor	Ionis Pharmaceuticals

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
AcroQoL	Acromegaly Quality of Life Questionnaire
AE	adverse event(s)
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ALS	acid labile subunit
aPTT	activated partial thromboplastin time
ASGPR	asialoglycoprotein receptor
ASO	antisense oligonucleotide
AST	aspartate aminotransferase (SGOT)
ASTS-M	Acromegaly Symptom and Treatment Score Questionnaire-Monotherapy
AUC_t	area under the plasma concentration-time curve from time zero to time t
βhCG	beta-subunit of human chorionic gonadotropin (pregnancy test)
BP	blood pressure
BUN	blood urea nitrogen
CKD-EPI	Chronic Kidney Disease-Epidemiological Collaboration
C_{max}	maximum concentration
CRA	Clinical Research Associate
CRF	case report form
CRNMB	clinically relevant non-major bleeding
CRP	C-reactive protein
CS	clinically significant
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
EBV	Epstein-Barr Virus
ECG	electrocardiogram
eCRF	electronic Case Report Form
ECHO	echocardiogram
EQ5D	Euro QOL
ETTX	early termination from treatment
ETPT	early termination from post-treatment
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	good clinical practice
GHBP	growth hormone binding protein
GH	growth hormone
GHR	growth hormone receptor
GHR-L_{Rx}	ISIS 766720

HbA1c	glycated hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
hs-CRP	CRP measured by high sensitivity assay
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor-1
IGFBP3	insulin-like growth factor binding protein 3
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
ISIS 766720	antisense inhibitor of GHR
MB	major bleeding
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically significant
NOAEL	no-observed-adverse-effect-level
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
on study	The patient is 'on study' from signing of the informed consent until their last study visit
OGTT	oral glucose tolerance test
PD	pharmacodynamic(s)
PE	physical examination
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PPS	per protocol set
PT	prothrombin time
PTWk5	Post-Treatment Week 5
QoL	quality of life
RNA	ribonucleic acid
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
SAE	serious adverse event
SF36	36-item Short Form Survey
siRNA	small interfering ribonucleic acid
SC	subcutaneous(ly)
Study Day 1	defined as the first day ISIS 766720 product is administered to the patient
Study Drug	ISIS 766720

SRL	somatostatin receptor ligands
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
T_{max}	time to maximal concentration
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
WBC	white blood cell
WOCBP	women of childbearing potential

1. OBJECTIVES AND ENDPOINTS

1.1. Objectives

1.1.1. Primary Objectives

To evaluate the safety and tolerability of ISIS 766720 subcutaneous (SC) injection as a monotherapy in patients with acromegaly.

To evaluate the efficacy of ISIS 766720 SC injection on serum insulin-like growth factor-1 (IGF-1) as a monotherapy in patients with acromegaly.

1.1.2. Secondary Objective

To evaluate the effect of ISIS 766720 SC to normalize serum IGF-1 levels.

[redacted]

1.2. Study Endpoints

1.2.1. Primary Endpoint

The primary efficacy endpoint is the percent change in IGF-1 from Baseline to Week 27.

1.2.2. Secondary Endpoints

The secondary efficacy endpoints include:

- Patients who achieve normalized IGF-1 levels to within 1.2 times gender and age limits at Day 183 (Week 27)
- Patients who achieve normalized IGF-1 levels to within 1.0 times gender and age limits at Day 183 (Week 27)
- Change from Baseline in serum IGF-1 over time
- Percent change from Baseline in serum IGF-1 over time

2. BACKGROUND AND RATIONALE

2.1. Overview of Disease

Acromegaly is a chronic disorder caused by GH hypersecretion, most commonly secondary to a GH secreting pituitary adenoma (Katznelson et al. 2014). Growth hormone circulates and through binding and activation of growth hormone receptor (GHR), it stimulates production of IGF-1. Circulating IGF-1 is mostly made in the liver (Liu et al. 2000); IGF-1 in large part mediates the somatic and metabolic effects of GH. Hypersecretion of GH leads to excess production of IGF-1 (Katznelson et al. 2014). High levels of circulating GH and IGF-1, lead to multisystem diseases due to somatic overgrowth and metabolic dysregulation, causing multiple comorbidities (e.g., type 2 diabetes, cardiomyopathy, and respiratory complications), premature mortality, physical disfigurement (e.g., enlarged facial features, hands, and feet, and painful arthritis), and decreased quality of life (QoL) (Melmed 2006; Giustina et al. 2020). Growth hormone hypersecretion worsens insulin resistance, producing impaired glucose tolerance and diabetes mellitus in 15-38% of patients (Katznelson et al. 2014). The incidence of acromegaly is approximately 3 cases per 1 million persons per year, and the prevalence is about 60 per million (Melmed 2006). The therapeutic goal for acromegaly includes normalization of biochemical variables (GH and IGF-1), reversal of mass effects of the tumor, improvement in signs, symptoms and comorbidities of the disease and minimization of long-term mortality risk. Treatment goals include assessment and management of the comorbidities, such as aggressive control of lipid abnormalities and type 2 diabetes (Katznelson et al. 2011; Katznelson et al. 2014).

Surgical removal of the pituitary tumor is the primary treatment for GH secreting adenoma. However, if the biochemical and clinical evaluation after surgery reveals persistent disease, or if surgery is not an option for the patient, then medical therapy is necessary. Current medical treatments include dopamine agonists, somatostatin receptor ligands (SRLs), and GHR antagonist (pegvisomant, or Somavert). According to societal guideline for acromegaly, (Katznelson et al. 2014), Somavert is recommended as a potential first line medication prior to combination therapy to treat persistent disease with or without surgery. In Phase 4 post-market observational studies, Somavert can normalize ~63% of the patients not previously controlled, however with the side effects of increased transaminases, and low incidence of adenoma growth (van der Lely et al. 2012; Tritos et al. 2017). In a retrospective analysis, Somavert monotherapy, administered either as primary medical therapy or as adjunctive therapy according to local practice, led to IGF-1 normalization in > 75% of patients (Tritos et al. 2017). As currently available medications are limited by incomplete efficacy and side effects that can include hyperglycemia, gastrointestinal upset, gallbladder disease, injection site reaction, or liver enzyme elevations, more safe and effective medical therapies are still needed.

2.2. Therapeutic Rationale

Since acromegaly is due to excessive GH and IGF-1 action, the goal is to suppress this pathway. As a matter of fact, normalization of circulating IGF-1 is a surrogate endpoint for the treatment of acromegaly. Inhibition of GH signaling results in suppression of IGF-1 secretion (Rowland et al. 2005). This can be achieved by suppressing the action of GHR. Clinical evidence that this mechanism lowers IGF-1 levels comes from studies conducted with Somavert (pegvisomant) and

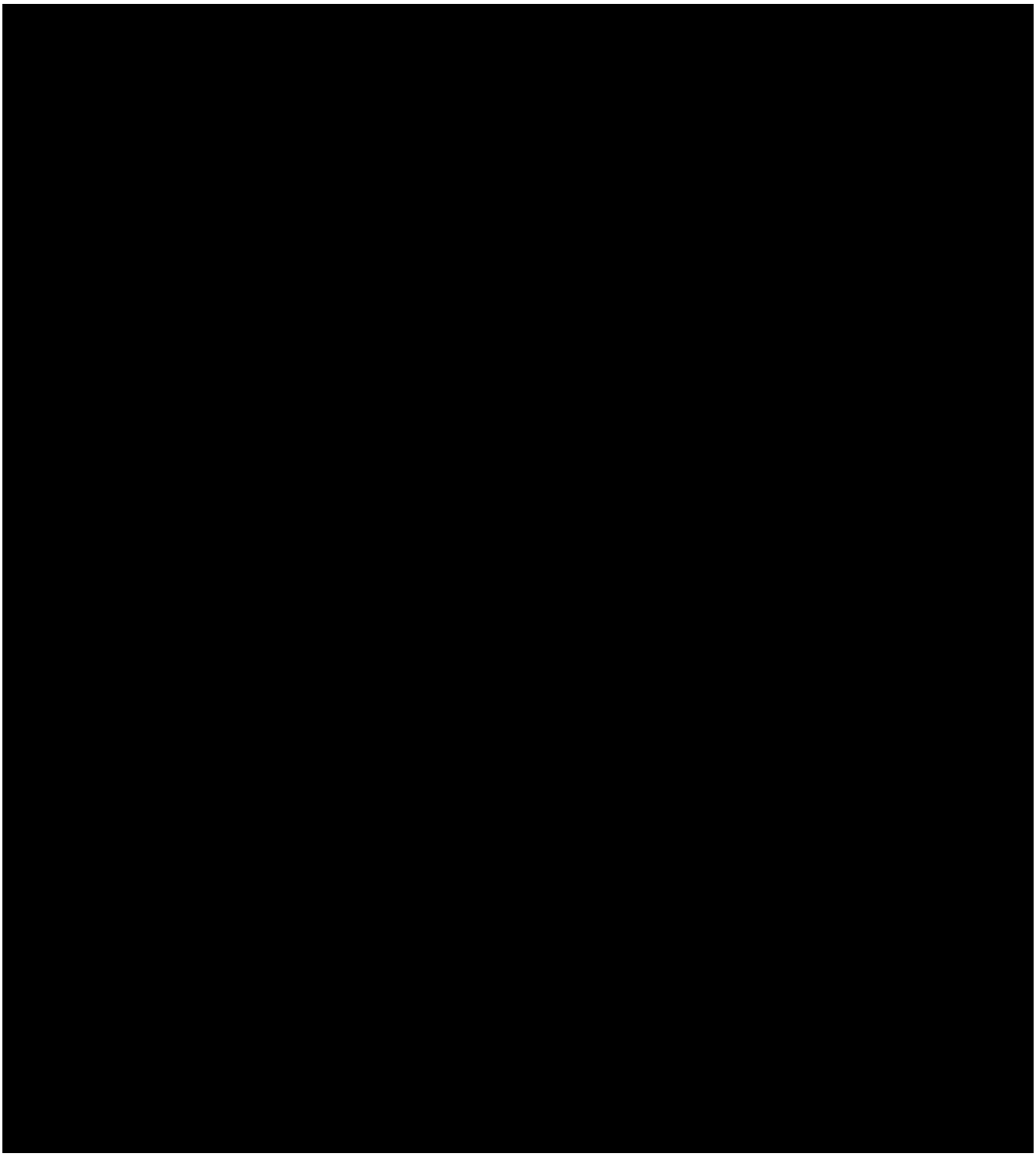
ATL1103. Somavert is a human GHR antagonist that competes with endogenous GH for binding to its receptor and blocks production of IGF-1, and can normalize IGF-1 in ~63% of patients. However, Somavert dosing regimen is inconvenient for patients as it requires daily administration by SC injection and it may also cause elevations in circulating GH levels and in liver transaminases (Melmed 2006). Additionally, clinical evidence of a reduction in IGF-1 levels by GH inhibition is supported by studies conducted with the antisense drug ATL1103 (an antisense inhibitor of GHR) in which ATL1103, by reducing GHR, reduced serum IGF-1 levels by 26% after 13 weeks of dosing (Trainer et al. 2018).

[redacted]In addition, since mature GHR is cleaved to produce the circulating GHBP which binds to circulating GH and prolongs its half-life (Fisker 2006), [redacted]

The known potential risks to study participants associated with ISIS 766720 are described in the Guidance to the Investigator section of the ISIS 766720 Investigator's Brochure.

2.3. ISIS 766720

[redacted]



2.3.4. Clinical Experience

Detailed information concerning the clinical studies conducted with ISIS 766720 can be found in the Investigator's Brochure. A summary is included below.

[redacted]

[redacted]

2.5. Benefit-Risk Assessment

Detailed information concerning the benefit-risk assessment of ISIS 766720 can be found in the Investigator's Brochure.

2.5.1. Benefit Assessment

The benefits of ISIS 766720 are unknown at this time.

[redacted]

[redacted]

3. EXPERIMENTAL PLAN

3.1. Study Design

This will be a Phase 2, randomized, open label multi-center study.

3.2. Number of Study Centers

This study will be conducted at multiple centers worldwide.

3.3. Number of Patients

Approximately 40 patients are planned to be randomized in the study. Thirty-six (36) patients (12 in each treatment group) in the per protocol set (PPS) are needed to complete the Treatment Period and the primary efficacy endpoint. [redacted]

3.4. Overall Study Duration and Follow-up

The study for an individual patient will generally consist of the following periods:

- A ≤ 6-week Screening Assessment Period
- A 73-week Treatment Period: ISIS 766720 will be administered as a once-monthly SC injection (except during Month 1 where a booster dose is administered on Day 15). The primary endpoint will be evaluated at 6 months (Week 27)
- A 14-week Post-Treatment Evaluation Period

Patients may be required to attend additional visits for monitoring of AEs or abnormal investigation results. The frequency of additional monitoring will be determined by the Sponsor Medical Monitor or Designee in consultation with the Investigator.

3.4.1. Screening

Patient eligibility for the study will be determined within 42 days prior to study entry. Sponsor Medical Monitor or Designee review is required for patients to enter the Treatment Period.

3.4.2. Treatment

Eligible patients will report to the Study Center for ISIS 766720 administration per Schedule of Procedures in Appendix A. ISIS 766720 will be dosed monthly (in addition, a booster dose of ISIS 766720 is administered on Day 15). Please refer to Section 6.1.2 and Appendix A for detailed instructions regarding treatment requirements.

3.4.3. Post-Treatment

Patients are to return to the Study Center for follow-up visits for 14 weeks after last injection of ISIS 766720 per Schedule of Procedures in Appendix A. Any patient who receives at least 1 dose of ISIS 766720 will be required to complete the Post-Treatment Period. The final study visit will be 14 weeks after the last injection (PTWk15).

4. PATIENT ENROLLMENT

4.1. Screening

Before patients may be enrolled into the study, the Sponsor or Designee requires a copy of the Study Center's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form (ICF), and all other patient information and/or recruitment material.

Patients or their legally acceptable representatives must sign the consent form before any screening tests or assessments are performed. At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including Screening procedures, are performed. At the time of randomization, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant

throughout the entire trial. In the event the patient is re-consented and re-screened the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.

4.2. Randomization

Patients will be randomized after all Screening assessments have been completed, after the Investigator has verified that they are eligible per criteria in Sections 5.1 and 5.2, and after review by the Sponsor Medical Monitor or Designee. No patient may begin treatment prior to randomization and assignment of a unique patient identification number.

[redacted]

4.3. Replacement of Patients

Patients who withdraw from the study will not be replaced.

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria at the time point specified in the individual eligibility criterion listed.

5.1. Inclusion Criteria

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements
2. Males or females with a documented diagnosis of Acromegaly* who are 18 to 75 years old (inclusive) at the time of informed consent

   * Defined as a previous diagnosis of GH-secreting adenoma by surgical pathology; or the presence of a pituitary adenoma identified on magnetic resonance imaging (MRI) or computed tomography (CT) Scan (if MRI is contraindicated) and serum IGF-1 levels above the upper limit of normal (ULN) for age and sex at time of diagnosis (serum IGF-1 level and imaging at diagnosis will be collected in the case report forms [CRF]).
3. Have had pituitary surgery (e.g. transsphenoidal) unless there was a contraindication to surgery **and** are either acromegaly medical treatment naïve, or who had not taken any other acromegaly medications prior to the screening visit as outlined below:

   bromocriptine: 2 weeks
   cabergoline: 4 weeks
   quinagolide: 4 weeks
   octreotide daily injection (SC) or oral formulation: 4 weeks
   pegvisomant: 4 weeks

octreotide LAR: 3 months
pasireotide LAR: 4 months
lanreotide (all formulations): 3 months

4. At Screening, serum IGF-1 (performed at central lab) between 1.3 to 5 × ULN, inclusive, adjusted for age and sex. IGF-1 can be repeated once and averaged to determine eligibility if the initial result is between 1.1–1.3 × ULN, or between 5–5.3 × ULN
5. Females must be non-pregnant and non-lactating, and either:
   a. surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
   b. post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone (FSH) levels in the postmenopausal range for the laboratory involved)
   c. abstinent (defined in Section 6.3.1) or
   d. Women of childbearing potential (WOCBP) should agree to taking all precaution to avoid pregnancy during the Trial Period (including Post-Treatment), including agreeing to receive pregnancy testing before each monthly dose, using 1 highly effective method of birth control (Section 6.3.1) from the time of signing the (ICF) until 14 weeks after the last dose of ISIS 766720 administration

   Males must be either:

   e. surgically sterile
   f. abstinent (defined in Section 6.3.1) or
   g. if engaged in sexual relations with a female of child-bearing potential, the patient must be using a highly effective contraceptive method (refer to Section 6.3.1) from the time of signing the ICF until 14 weeks after the last dose of ISIS 766720
6. Willing to refrain from strenuous exercise/activity (for example heavy lifting, weight training, intense aerobics classes etc.) for at least 24 hours prior to study visits
7. Willing to refrain from alcohol or tobacco use for 8 hours prior to study visits

5.2. Exclusion Criteria

1. Clinically significant (CS) abnormalities in medical history according to Investigator judgement (e.g., previous acute coronary syndrome within 6 months of Screening, major non-pituitary surgery within 2 months of Screening) or from Screening physical examination (PE)
2. Patients who received surgery for pituitary adenoma within the last 3 months before the trial, and/or planning to receive surgery during the trial
3. Patients who received radiotherapy for pituitary adenoma within the last 2 years before the trial, and/or planning to receive radiotherapy during the trial
4. Patients with a pituitary tumor that, per Investigator judgment, is worsening (e.g., either growing, or at risk of compressing or abutting the optic chiasm or other vital structures) as assessed by pituitary/sellar MRI protocol at Screening or within 3 months of Screening. CT scan is allowed if MRI is contraindicated

5. Evidence of decompensated cardiac function per medical judgement and/or New York Heart Association (NYHA) Class 3 or 4
6. Clinical evidence of symptomatic hyperprolactinemia that would necessitate treatment
7. Symptomatic cholelithiasis, and/or choledocholithiasis
8. Intentionally left blank
9. Patients with history of hypoglycemia unawareness (who have had > 3 severe episodes in the past 6 months) or documented reactive hypoglycemia
10. Screening laboratory results as follows, or any other CS abnormalities in Screening laboratory values that would render a patient unsuitable for inclusion (abnormalities may be retested for eligibility purposes)
    a. UPCR ≥ 500 mg/g. In the event of urine protein/creatinine ratio (UPCR) above this threshold eligibility may be confirmed by a quantitative total urine protein measurement of < 1000 mg/24 hr
    b. Positive test (including trace) for blood on urinalysis. In the event of a positive test eligibility may be confirmed with urine microscopy showing ≤ 5 red blood cells per high power field
    c. alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 × ULN; alkaline phosphatase (ALP) > 3 × ULN; Total bilirubin ≥ 1.5 × ULN. Patients with Gilbert's syndrome may have total bilirubin ≥ 1.5 × ULN if only the indirect bilirubin is elevated > ULN and the ALT/AST is not greater than the ULN.
    d. eGFR < 45 mL/min/1.73 m^2 as determined by the Chronic Kidney Disease-Epidemiological Collaboration (CKD-EPI) equation for creatinine clearance OR serum creatinine > 1.8 mg/dL in males and > 1.5 mg/dL in females
    e. Platelet count < 125,000 mm^3
    f. Abnormal thyroid function tests must be discussed with the Sponsor Medical Monitor or Designee
    g. HbA1c > 10%
    h. Abnormal morning cortisol test demonstrating symptomatic adrenal insufficiency based on Investigator judgement
11. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to Study Day 1
12. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator
13. Active infection with human immunodeficiency virus (HIV), hepatitis C (HCV) or hepatitis B (HBV) diagnosed by initial serology testing and confirmed with RNA testing, or prior treatment for HCV. Patients at Screening who test positive by serology, but negative by RNA may be allowed in consultation with the Sponsor Medical Monitor or Designee
14. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin, carcinoma *in situ* of the cervix, follicular Stage 1 or papillary thyroid cancer that has been successfully treated; patients that have been treated with curative intent and which have

no recurrence within 5 years may also be eligible if approved by the Sponsor Medical Monitor or Designee

15. Treatment with another investigational drug, biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
16. Treatment with any non-ION- or ISIS-oligonucleotide (including small interfering ribonucleic acid [siRNA]) at any time or prior treatment with an ION- or ISIS-oligonucleotide within 9 months of Screening. Patients that have previously received only a single-dose of an ION- or ISIS-oligonucleotide as part of a clinical study may be included as long as duration ≥ 4 months has elapsed since dosing. This exclusion does not apply to vaccines (neither mRNA nor viral vector vaccines)
17. History of bleeding diathesis or coagulopathy
18. Recent history of, or current drug or alcohol abuse that could affect study compliance per Investigator judgment
19. Patients may not have chronic systemic use of weight loss medications (except GLP-1 agonist or SGLT2 inhibitors) or participate in weight loss programs within 2 months before Screening. Patients taking GLP-1 agonist or SGLT2 inhibitors indicated for weight loss may be allowed with prior consultation with the Sponsor Medical Monitor or Designee
20. Patients on anti-diabetes medications must be on a stable dose and regimen for ≥ 3 months prior to Screening. Patients taking insulin can be allowed with prior consultation with the Sponsor Medical Monitor or Designee
21. Patients on estrogen containing medications must be on a stable dose and regimen for ≥ 3 months prior to Screening
22. Patients on glucocorticoid replacement used for adrenal insufficiency must be on a stable dose and regimen (increases used to prevent adrenal crisis is permitted) for ≥ 3 months prior to Screening
23. Use of oral anticoagulants, unless the dose has been stable for 4 weeks prior to the first dose of ISIS 766720 and regular clinical monitoring is performed during the trial
24. Blood donation of 50 to 499 mL within 30 days of Screening or of > 499 mL within 60 days of Screening and during the trial
25. Have any other conditions, which, in the opinion of the Investigator and Sponsor would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the Study

6. STUDY PROCEDURES

6.1. Study Schedule

All required study procedures are outlined in Appendix A, Appendix B, and Appendix C.

6.1.1. Screening

Written informed consent for the study will be obtained prior to the performance of any study-related procedures including screening procedures. Race and ethnicity data will be

collected as part of the demographic information for all screened patients during the Screening Period. Up to a 6-week Screening Period is provided for completing screening assessments and determining patient eligibility for the study.

During the 6 weeks, site will need to gather disease history relating to acromegaly and pituitary adenoma, and the results of the most recent MRI. MRI of the sellar will need to be performed before randomization if there is no prior MRI within the last 3 months prior to Screening. If the MRI is contraindicated, then a CT Scan may be performed. In addition, an echocardiogram will be conducted, if there is no prior echocardiogram within the last 3 months prior to Screening.

Individuals may be disqualified if the result of any laboratory test is outside the range specified in the eligibility criteria (Section 5.1 and 5.2) or, if no range is specified, is abnormal and CS as judged by the Investigator or the Sponsor Medical Monitor or Designee. During the Screening Period, screening results may be retested (Home Health Care Visit Option can be used) for assessment after discussion with the Sponsor Medical Monitor or Designee for eligibility purposes.

IGF-1 can be repeated once and averaged to determine eligibility if the initial result is between 1.1–1.3 × ULN, or between 5–5.3 × ULN.

Sponsor Medical Monitor or Designee review of eligibility is required for patients to enter the Treatment Period. Qualified patients will be randomized and proceed to the Treatment Period Week 1, Day 1 Assessments.

Screen failed patients may be re-screened 1 more time after the Investigator feels the reason for screen failure has resolved.

6.1.2. Treatment Period

During the 1.5-year study, each patient will receive up to 20 SC doses of ISIS 766720 with a planned monthly interval between each dose except for a booster dose at Day 15 (WK 3). All patients will have bi-weekly visits beginning at Day 1 (WK 1) through Day 113 (WK 17). After that visits occur monthly through Day 505 (WK 73) with an additional visit on Day 183 (WK 27) for primary endpoint assessments. Of the 24 required study visits, 14 selected study visits may be performed outside of the clinic by a Sponsor selected Home Health Care professional (See Appendix A). Home health visits are optional and would be arranged by study center staff if requested by the patient. In consultation with the Sponsor, a Home Health Care visit may be conducted for a study visit day that was intended to be an in-clinic visit. It is preferable that the entire visit is conducted, however the following assessments may be omitted: ECG, body weight, physical exam, ring size, and OGTT. If a visit cannot be performed in the clinic or by Home Health, patient contact (e.g., phone, text, email or video) is required by site personnel to assess any adverse events or changes in concomitant medications. Any assessments not completed at the Home Health Care visit should be attempted at the next clinic visit.

Safety, efficacy, PK and exploratory assessments will be performed per Appendix A, Appendix B, and Appendix C throughout the Treatment Period on ISIS 766720 administration days. At each visit, patients should arrive fasting at least 8 hours for safety and clinical laboratory evaluations; vital signs, blood pressure (BP) assessments, AEs and concomitant medication usage will be assessed during each visit.

A 2-hour OGTT and GH response procedure will be conducted pre-dose on Day 1 and pre-dose on Day 183 (WK 27) and Day 505 (WK 73). The pre-dose-Day 1 OGTT and GH response procedure may be conducted between Day -41 and pre-dose Day 1. To decrease the study burden on potential patients, it is suggested that this procedure is done after the patient has completed and qualified based on all other screening procedures. The OGTT and GH Response procedure can be conducted in the clinic or as arranged by a Home Health Care professional. The patient must fast 10-hours prior to OGTT and GH Response assessment.

Quality of life assessments and general health assessments including ASTS-M, AcroQOL, EQ5-D, and SF-36 questionnaires will be assessed along with ring size assessment periodically throughout the study. See Section 6.2.3 for a description of the study procedures. Study required procedures at study visits are listed in the Schedule of Procedures in Appendix A, Appendix B, and Appendix C. Patient will be requested to complete AcroQoL, ASTS-M, EQ5-D, and SF-36 and ring size assessments prior to all other procedures and dosing (see Section 6.2).

All blood samples should be drawn prior to ISIS 766720 administration (exceptions are the post-dose samples for PK sampling at Day 1 and Day 113).

An MRI (3×) and Echocardiogram (2×) will be done. See Appendix A for timing of procedure.

During each visit, the study staff should attempt to complete all the study procedures prior to ISIS 766720 administration as outlined in the Appendix A, however, if a procedure is conducted after ISIS 766720 administration it will be considered a deviation that does not impact the evaluation of efficacy.

All safety data including AEs and concomitant medications will be reviewed by the Sponsor's Medical Monitor or Designee on an ongoing basis throughout the trial. Early termination patients from the Treatment Period will be requested to enter the 14-week Post-Treatment Period. The first visit to complete is an "early termination from treatment" visit entitled ETTX. The ETTX visit should be completed as soon as possible after the decision is made, preferably 4 weeks after the last dose. The remainder of the Post-Treatment visits should then follow the schedule which are in intervals relative to the patients last dose (Appendix A). All patients receiving at least 1 dose of study medication are required to enter the Post-Treatment Period for continuing safety evaluations. Please contact your CRA at the time of early termination to review the schedule.

6.1.3. Post-Treatment Period

After completing the 73 weeks of the Treatment Period, including patients who discontinue early from the Treatment Period, patients will return for Post-Treatment follow-up evaluations (Appendix A). All patients will be followed for 14 weeks, the last visit is Post-Treatment Week 15 (PTWk15) occurring 99 days after the last dose. Note: the visits are scheduled in intervals relative to the patient's last dose, for example Post-Treatment Week 5 (PTWk5) is 28 days after the last dose.

Safety and clinical laboratory evaluations as well as PD markers, including those for PK/PD analysis, will be performed as indicated in the Appendix A, Appendix B, and Appendix C. Safety and efficacy data, including any AEs and concomitant medications will be recorded and reviewed by the Sponsor's Medical Monitor or Designee.

The AcroQoL, ASTS-M, EQ5-D, and SF-36 and ring size assessment will be conducted periodically in the Post-Treatment Period.

Early termination patients from the Post-Treatment Period (ETPT) will be required to complete the ETPT Study procedures (Appendix A).

6.2. Study/Laboratory Assessments

6.2.1. Clinical Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B. Blood chemistry should be taken after fasting for at least 8 hours (at least 10 hours for OGTT). During this time the patient should ensure that they consume sufficient water in order to not become dehydrated.

If the platelet value, serum creatinine or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing, a repeat blood specimen should be re-drawn as soon as possible (ideally within 7 days) either in clinic or by home health or local laboratory. The next dose of ISIS 766720 may not be administered until a result not meeting a stopping rule is available. See Section 8.5 for more guidance. Platelet results must meet the timeframe requirements in Section 8.5.2.

At any time, the Sponsor Medical Monitor or designee may request both a local and central laboratory collection in parallel to assess patient safety.

6.2.2. Oral Glucose Tolerance Test and Growth Hormone Response during OGTT

Patients will undergo OGTT and GH response procedures during the study per Appendix A. For each OGTT procedure, patients should be fasting for 10 hours before the test (only water is permitted). It is preferable to collect blood samples for OGTT through indwelling catheter, but it is not mandatory. (See Appendix A and Table 1). After an indwelling catheter (if used) is inserted at T-5 minutes, a 5-minute period is allowed to remove any effects linked to the stress induced by venipuncture. Blood sampling will begin before the glucose solution is consumed at Time 0. The glucose anhydrous solution (75 grams in a 300-mL solution) will be consumed within a 5-minute period, after which blood samples will be drawn during the test every 30 minutes from the start time of glucose ingestion during the 2 hours of the OGTT as outlined in Table 1. Patients may drink water during the OGTT but must refrain from eating or drinking any other fluids except water and must refrain from smoking until the fasting period is completed (after the 120-minute blood draw). During the Treatment Period, the OGTT should be completed before ISIS 766720 is administered.

Table 1: Sampling Schedule: Day of Oral Glucose Tolerance Test and GH Response During OGTT

Intervention	Time (Minutes)	OGTT and GH Response Sampling
	-5	Catheter Insertion (if used)
T_0 = 75 grams Glucose Ingestion	0 Prior to Glucose ingestion	Glucose, Insulin, C-peptide, Growth Hormone
	30	Glucose, Insulin, C-peptide, Growth Hormone
	60	Glucose, Insulin, C-peptide, Growth Hormone
	90	Glucose, Insulin, C-peptide, Growth Hormone
	120[#]	Glucose, Insulin, C-peptide, Growth Hormone

[#] After the 120-min blood draw, the fasting period is completed

6.2.3. Assessments for Acromegaly

There are up to 5 procedures that will be conducted that assess signs, symptoms and QoL for an acromegaly patient. For purposes of this clinical trial and consistency across visits, it is requested that these assessments for acromegaly be:

1. Conducted at the beginning of the study visit (prior to other study procedures and drug administration)
2. Conducted sequentially in this order: 1) AcroQoL; 2) ASTS-M; 3) EQ-5D; 4) SF-36; 5) Ring Size Assessment. All QOL and health assessment questionnaires will be a paper assessment filled out by patients and the results are entered into eCRF by site staff
3. It may take approximately 40 minutes to complete all 5 assessments

Prior to filling out the QOL and health assessment questionnaires, the patient should sit quietly in a room without distraction, and be reminded of the following; i) the purpose of the questionnaires, ii) to complete the questionnaire honestly, and iii) they should be aware that there are no wrong answers, iv) it is important to answer all questions.

Note: the order of completion of assessments relative to ISIS 766720 administration is a recommended best practice but not a requirement, and therefore will not constitute a deviation if not strictly followed.

6.2.3.1. Acromegaly Quality of Life Questionnaire

To assess the health-related QoL affected by acromegaly, patients will complete the AcroQoL questionnaire during the Treatment and Post-Treatment Periods (per Appendix A). AcroQoL is a 22-question survey to quantify the self-perceived impact of acromegaly in patients' life. It contains 2 scales that evaluate physical (8 questions) and psychological aspects related to the appearance and personal relations (7 items each) (Webb et al. 2002). This questionnaire will take about 10 minutes to be completed.

6.2.3.2. Acromegaly Symptoms and Treatment Score Questionnaire-Monotherapy

Patients will be asked to complete the ASTS-M to monitor symptoms relating to acromegaly and its treatments. Each question is answered on a scale of 0 to 4 from no symptom to very severe. The questions address acromegaly-specific symptoms (e.g., headache, perspiration, paresthesia) and treatments (burden of ISIS 766720). This questionnaire will take about 5 minutes to complete.

6.2.3.3. EQ-5D

Patients will be asked to complete the EQ5D which is a standardized instrument for measuring health outcome. It measures 5 health dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety depression. It is used as a quantitative measure of health outcome that reflects the patient's own judgement. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This questionnaire will take about 10 minutes to complete.

6.2.3.4. 36-Item Short Form Survey

Patients will be asked to complete the SF-36 which is a set of generic, coherent, and easily administered QoL measures. It measures 8 health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. Each section has different instructions on how to answer the questions. This questionnaire will take about 10 minutes to be completed.

6.2.3.5. Ring Size Assessment

Finger size is an objective measure of soft tissue swelling and overgrowth and can be used to monitor the response to treatment. Measurement should be taken prior to any intravenous cannulation. Ring size is assessed using the study provided ring sizer widget and the 4th finger of the non-dominant hand. The ring size to record is the one with the tightest fit. If the finger is too large to be measured by the ring sizer then use the 5th finger (and make a note of this). The same finger will be used throughout the trial (Barts Endocrine 2009). The ring size assessment should be completed by the same staff member at each visit if possible.

6.2.4. MRI

MRI of the sellar region will be conducted for all patients for whom MRI is not contraindicated, e.g., patients having metal implants. If the MRI is contraindicated, then a CT scan may be performed. See Appendix A for timing of procedure.

6.2.5. Echocardiography

Echocardiography for assessment of left and right ventricular function be conducted at times indicated in Appendix A. For the purpose of assessment of treatment-emergent changes, all echocardiograms will be evaluated by an independent central reader.

6.3. Restriction on the Lifestyle of Patients

6.3.1. Contraception Requirements

All male patients and WOCBP must refrain from sperm/egg donation and practice highly effective contraception from the time of signing the ICF until 14 weeks after their last dose of study treatment.

Male patients engaged in sexual relations with a female of child-bearing potential must use highly effective contraception from the time of signing the informed consent until 14 weeks after the patient's last dose of study treatment. If the patient's s non-pregnant female partner is using a highly effective contraception method throughout the duration of the study, the requirement for contraception for the male patient is considered fulfilled.

For the purposes of this study, WOCBP are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

For the purposes of the study, highly effective contraception is defined as follows:

For male patients:

- a vasectomy with negative semen analysis at Follow-up
- sexual abstinence†
- Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to the ISIS 766720

For female patients of childbearing potential:

- surgical sterilization (e.g., bilateral tubal occlusion), hormonal contraception associated with inhibition of ovulation (combined [estrogen and progestogen containing] or progestogen-only), intrauterine device (IUD), intrauterine hormone-release system (IUS), a vasectomized partner or sexual abstinence†

† **Note:** Abstinence is only acceptable as true abstinence, refraining from heterosexual intercourse throughout the duration of study participation. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception.

Note: A female condom and a male condom should not be used together as friction between the 2 can result in either or both products failing.

6.3.2. Other Requirements

Patients must refrain from strenuous exercise/activity (for example heavy lifting, weight training, intense aerobics classes etc.) for at least 24 hours prior to each study visit and also be willing to refrain from alcohol or tobacco use for 8 hours prior to study visits and/or laboratory sampling.

All patients will be required to fast for at least 8 hours before laboratory sampling and for at least 10 hours before OGTT and GH response assessments.

7. STUDY DRUG

7.1. Study Drug Description

[redacted]

7.2. Packaging and Labeling

The Sponsor will provide the Investigator with packaged ISIS 766720 labeled in accordance with specific country regulatory requirements.

7.3. Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of ISIS 766720 supplies provided by the Sponsor according to Sponsor instruction and in accordance with institutional policy.

8. TREATMENT OF PATIENTS

[redacted]

[redacted]

8.2. Other Protocol-Required Drugs

There are no other protocol related drugs for this study.

8.3. Other Protocol-Required Treatment Procedures

There are no other protocol required treatment procedures.

8.4. Treatment Precautions

There are no specific treatment precautions required for this study.

8.5. Safety Monitoring Rules

Please refer also to the 'Guidance for Investigator' section of the Investigator's Brochure.

For the purposes of safety monitoring Baseline is defined as:

- Monitoring Rules for Liver Chemistry Tests, Renal parameters, and Platelets – Unless otherwise specified, baseline is defined as the average of pre-dose values

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations for ISIS 766720 as well as other ASOs.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 7 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the re-test **must be available** prior to administering the next dose of ISIS 766720.

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the re-test results are available. In general, patients who do not meet the

stopping rules based upon re-test may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified Designee) should confer as to whether additional close monitoring of the patient is appropriate. If any of the stopping criteria described in Section 8.6 are met, the patient will be permanently discontinued from further treatment with ISIS 766720, evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor (or appropriately qualified Designee), and will be followed up in accordance with Section 8.8 of the Protocol.

8.5.1. Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 × ULN or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional, confirmatory measurements should also be performed if ALT or AST levels increase to 5 × ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 × ULN or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN should have their liver chemistry tests (ALT, AST, ALP, international normalized ratio [INR], and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.5 × ULN or < 1.5 × baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 × ULN or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN, the following evaluations should be performed:

1. Obtain a more detailed history of symptoms and prior and concurrent diseases
2. Obtain further history for concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
3. Obtain a history for exposure to environmental chemical agents and travel
4. Serology for viral hepatitis (hepatitis A virus [HAV] immunoglobulin M [IgM], hepatitis B surface antigen [HBsAg], HCV antibody, cytomegalovirus [CMV] IgM, and Epstein-Barr Virus [EBV] antibody panel)
5. Serology for autoimmune hepatitis (e.g., antinuclear antibody)

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic CT or MRI scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor or Designee. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 × ULN.

8.5.1.1. Dose Adjustment Guidelines for Liver Monitoring

Patients with a confirmed ALT or AST ≥ 3 × ULN but ≤ 5 × ULN without an alternative explanation, with normal bilirubin levels, and who have not met other stopping rules, may have their ISIS 766720 adjusted downward in consultation with the Sponsor Medical Monitor or Designee.

Dose adjustment will not be allowed for patients with confirmed elevations > 5 × ULN. These patients will follow steps outlined in Section 8.6 Stopping Rules.

8.5.2. Safety Monitoring Rules for Platelet Count Results

An evaluable platelet count is required prior to each dose during the Treatment Period. Treatment should be held if there is no evaluable platelet count within the 2 weeks (+7 days) up to Week 17 and within 4 weeks (+7 days) after Week 17 prior to the scheduled dose. Any unreportable platelet count result must be rechecked and determined not to have met a stopping rule before dosing can continue. Central laboratory is preferred; however, a local laboratory may be utilized to ensure a platelet value is available prior to dosing.

If a patient's absolute platelet count is ≥ 75,000/mm^3 to ≤ 100,000/mm^3, then the patient's platelet counts should be monitored weekly. In case of platelet count below 75,000/mm^3, the platelet monitoring rule defined in Stopping Rules (Section 8.6.3) should be followed.

In the event of a platelet count < 75,000/mm^3, additional laboratory investigations may be conducted in consultation with Sponsor Medical Monitor or Designee.

8.5.3. Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding (MB) or clinically relevant, non-major bleeding events (which are defined in Section 8.6.3). If a minor bleeding event occurs, additional testing of coagulation parameters (activated partial thromboplastin time [aPTT], prothrombin time [PT], INR) and platelet count may be performed after consultation with the Sponsor Medical Monitor or Designee.

8.5.4. Safety Monitoring Rules for Renal Function Test Results

If a patient's results meet Criteria 1 or 2 below, please confirm the results and initiate weekly monitoring if confirmed. If the event of a persistent elevation is observed over 2 consecutive weeks, then go to Section 8.6.2.

1. Serum creatinine increase that fulfills all of the following: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN (refer to definition of baseline in Section 8.6)
2. Proteinuria, UPCR > 750 mg/g for baseline > 200 mg/g, or 4 × baseline for baseline < 200 mg/g that is confirmed by repeated UPCR or by a quantitative total urine protein measurement of > 1.0 g/24 hr

8.6. Stopping Rules

For the purposes of the stopping rules baseline is defined as: the average of pre-dose values (unless otherwise specified).

8.6.1. Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor** (or appropriately qualified Designee)**,** dosing of a patient with ISIS 766720 will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 × ULN, which is confirmed
2. ALT or AST > 5 × ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 × ULN or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN, which is confirmed **and** total bilirubin > 2 × ULN or INR > 1.5
4. ALT or AST > 3 × ULN or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN with the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia (> ULN)

8.6.2. Stopping Rules for Renal Function Test Results / Temporary Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for either of the 2 criteria below, dosing of a patient with ISIS 766720 will be suspended temporarily:

1. Serum creatinine increase that fulfills all of the following: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN (refer to definition of baseline in Section 8.6)
2. Proteinuria, UPCR > 750 mg/g for baseline > 200 mg/g, or 4 × baseline for baseline < 200 mg/g that is confirmed by repeated UPCR or by a quantitative total urine protein measurement of > 1.0 g/24 hour

The possible dosing re-initiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or Designee.

8.6.3. Stopping Rule for Platelet Count Results

In the event of any platelet count less than 50,000/mm^3, dosing of the patient with ISIS 766720 will be stopped permanently. Platelet count will be monitored at least twice weekly until 3 successive values > 75,000/mm^3 then weekly until 3 values > 100,000/mm^3 (Table 4).

Administration of steroids is recommended for patients whose platelet count is less than 25,000/mm^3. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days.

Note: Patient may require continuation with oral steroids after methylprednisolone treatment is stopped.

In the event of a platelet count < 75,000/mm^3 and > 50,000/mm^3, and in the absence of MB or clinically relevant non-major bleeding (CRNMB) (defined below; (Schulman and Kearon 2005; Buller et al. 2007) , dosing with ISIS 766720 should be suspended temporarily until the platelet count has recovered to > 100,000/mm^3. The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Sponsor Medical Monitor or Designee and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced, and the speed of recovery of platelet count after interruption of dosing. If dosing is reinitiated, platelet count must be measured weekly until the end-of-study.

If, after reintroduction of ISIS 766720, the platelet count falls below 75,000/mm^3, further dosing of the patient with ISIS 766720 will be stopped permanently.

Definition of Major Bleeding Events (Schulman and Kearon 2005):

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome
3. Clinically overt bleeding leading to transfusion of ≥ 2 units of packed red blood cells or whole blood or a fall in hemoglobin of 2.0 mg/dL (1.24 mmol/L) or more within 24 hours

Definition of Clinically Relevant Non-Major Bleeding Events (Buller et al. 2007):

Clinically relevant CRNMB is defined as overt bleeding not meeting the criteria for MB but that resulted, for example, in medical examination, intervention, or had clinical consequences for a patient.

Definition of Minor Bleeding Events:

Minor bleeding events are those that do not fulfill the criteria for MB or CRNMB (defined above).

Table 4: Actions in Patients with Low Platelet Count

Platelet Count	Drug Dose	Monitoring
> 100,000/mm^3	No action	Monitor per Schedule of Procedures every 2 weeks (+7 days) up to Week 17 and every 4 weeks (+7 days) after Week 17
≥ 75,000 to ≤ 100,000/mm^3	No action	Monitor every week until 3 successive values > 100,000/mm^3
≥ 50,000 to < 75,000/mm^3	Pause dosing When platelet count returns to > 100,000/mm^3 restart dosing **only if approved by Sponsor Medical Monitor** or Designee	Monitor at least twice weekly until 3 successive values > 75,000/mm^3 then weekly until 3 values > 100,000/mm^3. If redosing then continue to monitor weekly for the remainder of the Treatment Period. If not redosing then subsequent monitoring should be per the Schedule of Procedures. Consider discontinuation of antiplatelet agents/ non-steroidal anti-inflammatory drug (NSAIDS)/anticoagulant medication while platelet count < 75,000/mm^3.
≥ 25,000 to < 50,000/mm^3	Permanently discontinue ISIS 766720	Monitor twice weekly until 3 successive values > 75,000/mm^3 then weekly until 3 values > 100,000/mm^3. Subsequent monitoring should be per the Schedule of Procedures. Discontinue antiplatelet agents/NSAIDS/ anticoagulant medication while platelet count < 75,000/mm^3 if possible.
< 25,000/mm^3	Permanently discontinue ISIS 766720	Monitor daily until 3 successive values show improvement then monitor twice weekly until 3 successive values > 75,000/mm^3 then weekly until 3 values > 100,000/mm^3. Subsequent monitoring should be per the Schedule of Procedures. Steroids recommended* Consider need for hospitalization and referral to hematologist Discontinue antiplatelet agents/ NSAIDS/ anticoagulant medication while platelet count < 75,000/mm^3 if possible

* Recovery in platelet count may be accelerated by administration of high-dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend Dexamethasone 40 mg daily for 4 days every 2-4 weeks for 1-4 cycles; Prednis(ol)one 0.5-2 mg/kg/d for 2-4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (note: may require continuation with oral steroids after methylprednisolone).

8.7. Adjustment of Dose and/or Treatment Schedule

ISIS 766720 dose adjustments and interruptions will be allowed for safety, tolerability or efficacy. Dose adjustments for efficacy (no higher than a 200 mg dose) may be made after Week 17 IGF-1 results are available. It is recommended to maintain an adjusted dose for efficacy for 3 months prior to further adjustment. Any dose adjustment requires consultation with the Sponsor Medical Monitor or Designee.

Patients may have their dose interrupted in response to AEs after consultation with Sponsor Medical Monitor or Designee.

8.8. Discontinuation of Study Drug/Treatment

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of ISIS 766720
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Sections 8.6.1 to 8.6.3
- The patient meets any of the following Exclusion Criteria (see Section 5.2) after discussion with the Sponsor Medical Monitor (or appropriately qualified Designee)
  - Patient needing pituitary surgery or radiation during Treatment Period
  - Patient with a pituitary tumor that is worsening (e.g., either growing, or at risk of compressing or abutting the optic chiasm or other vital structures) as assessed by pituitary/sellar MRI protocol
  - Treatment with any other acromegaly medications

The reason for discontinuation of ISIS 766720 must be recorded in the electronic Case Report Form (eCRF) and source documentation.

Patients who discontinue ISIS 766720 should complete early termination from treatment visit (ETTX) and then enter the Post-Treatment Period) unless consent is withdrawn. Minimally, every effort should be made to complete the ETTX (see Appendix A, Section 6.1.2).

If the patient declines or is unable to participate in the above, the Investigator should clarify what type of follow-up the patient is agreeable to: in person, by phone/mail, through family/friends, via correspondence/communication with other physicians, and/or from review of the medical records. Wherever possible, these patients should continue to be followed up via the agreed means to collect information on AEs, concomitant medications and survival status. At the very least, the patient's status at the end of the protocol defined study period should be ascertained and documented wherever possible. The agreed means of follow-up will be documented in the patient records and the Sponsor notified.

8.9. Withdrawal of Patients from the Study Procedures

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study Procedures might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the eCRF.

Any patient who withdraws consent, in writing or via verbal communication (documented by study site personnel) to participate in the study will be removed from further treatment and study observation immediately upon date of request. These patients should be encouraged to complete the ETTX visit procedures at the time of withdrawal if patient is in the Treatment Period, or the ETPT visit if patient is in the Post-Treatment Period (Appendix A). If the patient declines or is unable to participate in the above, the Investigator should clarify what type of follow-up the patient is agreeable to: in person, by phone/mail, through family/friends, via correspondence/ communication with other physicians, and/or from review of the medical records. Wherever possible these patients should continue to be followed up via the agreed means to collect information on AEs, concomitant medications and survival status. At the very least, the patient's status at the end of the protocol defined study period should be ascertained and documented wherever possible. The agreed means of follow-up will be documented in the patient records and notified to the Sponsor.

For patients withdrawn for reasons other than withdrawal of consent every effort should be made to complete the Post-Treatment Period and early termination study procedures.

8.10. Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's eCRF. Adverse events related to administration of these therapies or procedures must also be documented on the appropriate eCRF.

8.10.1. Concomitant Therapy

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between signing of informed consent and last visit (PTWk15/ETPT).

Allowed Concomitant Therapy

Any other medications deemed necessary by the Investigator are allowed except those listed in the disallowed concomitant therapy.

In the Post-Treatment Period, approved acromegaly medication may be added for patients with elevated IGF-1 (≥ 1.3) levels in consultation with the Investigator and Sponsor Medical Monitor or Designee.

Disallowed Concomitant Therapy

The following medications or interventions cannot be started during the Treatment Period: other approved or investigational medications for acromegaly (e.g., bromocriptine, cabergoline, pasireotide, quinagolide, octreotide (all formulations), pegvisomant, pasireotide, lanreotide (all formulations), dopamine agonist). If modification of acromegaly medication is considered, the recommendation is to wait until after Week 17 to allow ISIS 766720 to reach steady-state therapeutic concentrations and to ensure patient is on a maximal dose of ISIS 766720 per Section 8.7 prior to initiation of other acromegaly medications.

Use of anti-obesity agents or weight loss programs are not allowed prior to Week 27. Initiation of anti-obesity agents or weight loss programs after Week 27 may be considered after consultation with the Sponsor Medical Monitor or Designee

It is preferred for patients to maintain stable regimens of estrogen containing medications, antidiabetic medications and glucocorticoids throughout the study, however, changes to a stable regimen allowed at Screening may only be considered after consultation with the Sponsor Medical Monitor or Designee.

Any investigational therapeutic drug or device including other marketed agents at experimental dosages/utilities that are being tested—patient will be withdrawn.

8.10.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between signing of informed consent and the last visit (PTWk15)

Surgery and radiotherapy for pituitary adenoma during the trial is not allowed (see Section 5.2) and patients who undergo these procedures during the study will be early terminated from the Treatment Period and enter the Post-Treatment Period.

8.11. Treatment Compliance

There is not a patient diary for this trial.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1. Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor or Designee in accordance with the applicable Ionis and/or Designee SOPs throughout the conduct of the clinical trial.

9.2. Regulatory Requirements

The Sponsor or Designee is responsible for regulatory submissions and reporting to the Investigators of serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH GCP. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations.

In addition to the Investigator's assessment of relatedness, the Sponsor or Designee will evaluate the available information and perform an independent assessment of all reported SAEs and determine if there is a reasonable possibility that ISIS 766720 is causally related to a reported SAE. While the Sponsor may upgrade an Investigator's decision it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

For the purpose of regulatory reporting of SUSARs, no SAE associated with use of ISIS 766720 is considered expected for this study population.

9.3. Definitions

9.3.1. Adverse Event

An adverse event (AE) can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not the AE is considered related to the medicinal (investigational) product.

An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at Baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from ISIS 766720

Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

9.3.2. Adverse Drug Reaction and Suspected Unexpected Adverse Drug Reaction

Adverse Drug Reaction (ADR)

In the *pre-approval* clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not have been established, ADR is defined as follows:

> All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

The phrase "responses to a medicinal product" means that a causal relationship between the medicinal product and the AE has been determined by the Sponsor as at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Suspected Unexpected Adverse Drug Reaction

A suspected unexpected ADR is any ADR, the nature or severity of which is not consistent with the applicable product information, e.g., Investigator's Brochure for an unapproved medicinal (investigational) product.

A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3. Serious Adverse Event (SAE)

A SAE is any AE that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

  An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization

  Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; the event itself may be of relatively minor medical significance [such as severe headache without any further findings]).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

9.3.4. Adverse Event of Special Interest

Adverse events of special interest (AESI), including both serious or non-serious events, is 1 of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor could be appropriate.

For the purpose of this study, severe reductions in platelet count < 50,000/mm^3 accompanied by a major MB event or CRNMB event, or platelet count of < 25,000/mm^3 independent of an MB or CRNMB event are considered as AEs of special interest and is subject to 15-day expediting reporting by the Sponsor to the regulatory agencies.

Investigators should report AEs that met the AESI criteria to the Sponsor immediately, and no more than 24 hours of the Investigator's first knowledge of the event.

9.4. Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible. Before a diagnosis is confirmed, all symptoms should be reported as separate AEs.

9.4.1. Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements, all SAEs, and any case of platelet count < 50,000/mm^3 (regardless of their relationship to ISIS 766720) should be reported to the Sponsor or Designee within 24 hrs of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the ICF and stops at the end of the patient's Follow-up Period which is defined as Early Termination Post-Treatment (ETPT) or Post-Treatment Week 15 (PTWK15) visit. When the Investigator is reporting by telephone, it is important to speak to someone in person vs. leaving a message. The Initial Serious Adverse Event Form should be completed, and a copy should be emailed or faxed to the Sponsor or Designee.

Detailed information should be actively sought and included on follow-up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2. Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the ICF and will stop at the end of the patient's Follow-up Period, which is defined as PTWk15/ETPT visit, or the last visit when patient withdraws consent. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

9.4.3. Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the Adverse Event CRF:

9.4.3.1. Relationship to the Study Drug

The event's relationship to ISIS 766720 is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of ISIS 766720, e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and ISIS 766720 administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to ISIS 766720 administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and ISIS 766720

9.4.3.2. Severity

The severity of AEs and SAEs relating to laboratory tests and AEs at the injection site will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3. Action Taken with Study Drug

Action taken with ISIS 766720 due to the event is characterized by 1 of the following.

- **None:** No changes were made to ISIS 766720 administration and dose
- **Not Applicable:** SAE/AE was reported during Screening Period prior to ISIS 766720 administration
- **Permanently Discontinued:** ISIS 766720 was discontinued and not restarted
- **Temporarily Interrupted, Re-started – Same Dose:** Dosing and/or dosing frequency was temporarily interrupted/changed or delayed due to the AE and restarted at the same dose
- **Reduced Dose:** Dosing was reduced, temporarily interrupted or delayed due to the AE and restarted at the next lower dose or reduced dosing frequency

9.4.3.4. Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form. Treatment should also be recorded on the concomitant treatment or ancillary procedures eCRF, as appropriate.

9.4.3.5. Outcome of the Adverse Event

If the event is a non-serious AE, then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity (if applicable):** AE severity changed

If the event is an SAE, then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Recovered with Sequelae:** The signs/symptoms of the reported SAE have improved but not completely resolved, and a new baseline for the patient is established since full recovery is not expected
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)
- **Unknown:** The outcome of the reported SAE is not available, e.g., patient is lost to follow-up

9.4.3.6. Follow-up of Adverse Event

Investigator Follow-Up

During the Study Period, the Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to ISIS 766720 or related to study procedures until a final outcome can be reported.

Resolution of AE (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

Investigator should follow-up, or support the Sponsor's effort to follow up with all pregnancies reported during the study from either the study patient or the female partner of male study patient until pregnancy outcome is available.

Sponsor Follow-Up

For SAEs, AESI and pregnancy cases in patients who has completed or terminated study, the Sponsor or a Designee should follow-up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

9.5. Procedures for Handling Special Situations

9.5.1. Abnormalities of Laboratory Tests

Clinically significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor or Designee. Laboratory abnormalities deemed not clinically significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study

- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3. Dosing Errors

ISIS 766720 errors (including overdose, underdose, and administration error) should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing CRF. If the patient takes a dose of ISIS 766720 that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of ISIS 766720 should be recorded on the Adverse Event eCRF. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Should an overdose occur, the Investigator or Designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or Designee within 24 hours.

9.5.4. Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a female patient becomes pregnant or a pregnancy is suspected, or if a male patient believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or Designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported by designating as 'Follow-up' on the Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with ISIS 766720. However, the patient will be encouraged to complete the Post-Treatment follow-up portion of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will

be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records to obtain additional information relevant to the normality of the newborn(s)**.** A longer follow-up may be required if the newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations; e.g., pregnancy ICF may be required.

Male patients: The progress of the pregnancy of a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, **the Study Center and Sponsor may follow-up with the mother and may request access to the mother and infant's medical records** to obtain additional information relevant to the pregnancy progress and outcome. A longer follow-up may be required if a newborn-child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations; e.g., partner ICF may be required.

10.3. Populations

Safety Set: All patients who are randomized and receive at least 1 dose of ISIS 766720.

Full Analysis Set (FAS): All randomized patients who receive at least 1 dose of ISIS 766720 and have at least 1 post-baseline efficacy or PD assessment.

Per Protocol Set (PPS): All FAS patients who complete at least 6 of the 8 doses of ISIS 766720 with the first 27 Weeks administered and have no significant protocol deviations that would be expected to impact efficacy.

PK Set: All patients who are randomized and receive at least 1 dose of ISIS 766720 and have at least 1 evaluable PK sample.

10.4. Definition of Baseline

Unless otherwise specified, baseline is defined as the last non-missing value prior to the first administration of ISIS 766720.

10.5. Interim Analysis

An interim analysis may be conducted when approximately 50% of patients complete the primary efficacy assessment.

10.6. Planned Methods of Analysis

Descriptive summary statistics including n, mean, median, standard deviation, interquartile range (25^{th} percentile, 75^{th} percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% type I error rates unless otherwise stated.

The efficacy endpoints will be assessed on the FAS and PPS with the latter being the basis for the primary efficacy analysis. The safety analyses will be performed on the Safety Set. Pharmacokinetic analysis will be conducted in the PK Set.

10.6.1. Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized using descriptive statistics by treatment group. Patient randomization and disposition will be summarized by treatment group. All patients enrolled will be included in the summary of patient disposition.

10.6.2. Safety Analysis

Treatment duration and amount of ISIS 766720 received will be summarized by treatment group and total. The TEAEs and serious TEAEs will be summarized for each treatment group and total using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system, by system organ class, preferred term, relationship to ISIS 766720, and severity. Tables and/or narratives of treatment-emergent deaths, serious and significant AEs, including early withdrawals due to AEs, will also be provided.

Laboratory tests including chemistry panel, complete blood count with differential, coagulation panel, complement etc., will be summarized by study visits for each treatment group and total. These safety variables will also be presented as change and percent change from Baseline over time after ISIS 766720 administration, as appropriate. Vital sign, calculated BMI, and ECG measures will be summarized by treatment group and total. Concomitant medications will be coded using WHO Drug dictionary and summarized as well.

Echocardiograms will be assessed by an independent central reader. Change from baseline will be summarized for the following parameters, that may include left ventricular mass (LVM), LVM index (LVMi), LV ejection fraction, LV posterior wall thickness (LVPWT), peak velocity ratio (E/A), interventricular septum thickness (IVST) and isovolumic relaxation time (IVRT) whenever possible.

10.6.3. Efficacy Analysis

The primary analysis will be the comparison of percent change from Baseline to Week 27 in serum IGF-1. The null hypothesis of no percentage change in serum IGF-I levels from Baseline to Week 27 will be tested for each treatment group in the PPS. The data will be analyzed using a one-sample t-test with an alpha level of 5%. Ninety-five percent (95%) confidence interval of estimated percent reduction within treatment group will also be provided. In the case data departs substantially from normality, the nonparametric test will be employed instead. The primary analysis will take place after all patients complete Treatment Period and the database has been locked.

The primary efficacy endpoint will also be assessed, as a secondary analysis, in the FAS.

Additional secondary efficacy analyses are:

- change and percent change from Baseline to each schedule post-baseline visit in serum IGF-1 by the ISIS 766720 treatment groups in the PPS and FAS. The data will be analyzed in a similar way to the primary analysis
- proportion of patients achieve normalized IGF-1 levels to within 1.2 times of gender and aged limits within each ISIS766720 treatment groups will be assessed by an exact binomial test in the PPS and FAS.
- proportion of patients achieve normalized IGF-1 levels to within 1.0 times of gender and aged limits within each ISIS 766720 treatment groups will be assessed by an exact binomial test in the PPS and FAS

[redacted]

Further details will be described in the Statistical Analysis Plan (SAP).

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1. Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor or Designee.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or ISIS 766720 are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the ICF should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed ICF should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2. Ethical Conduct of the Study

All applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements must be followed.

11.3. Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed ICF, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and ICF must be received by the Sponsor before recruitment of patients into the study and shipment of ISIS 766720. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by

the Sponsor before recruitment of patients into the study and shipment of ISIS 766720. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of SAEs occurring at the Study Center and other AE reports received from the Sponsor or Designee, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor.

11.4. Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the CRFs or other documents submitted to the Sponsor, patients should be identified by initials (if permitted by local law) and a patient identification number only. Documents that are not for submission to the Sponsor (e.g., signed ICFs) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1. Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor.

12.2. Study Termination

The Sponsor reserves the right to terminate the study. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor should notify the IEC/IRB in writing of the trial's completion or early termination.

12.3. Study Documentation and Storage

An eCRF utilizing an Electronic Data Capture application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, imaging, and correspondence. In this study, eCRF may not be used as source documents.

The Investigator and Study Center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor
- If drug supplies are maintained at the Study Center, proof of receipt, ISIS 766720 Product Accountability Record, Return of ISIS 766720 Product for Destruction, final ISIS 766720 product reconciliation, and all drug-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor.

12.4. Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor or Designee is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department (or Designees). Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor or Designee. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor or Designee.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

12.5. Language

Case report forms must be completed in English. Generic names and trade names are acceptable for concomitant medications. Combination medications should be recorded using their trade name.

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

12.6. Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

13. REFERENCES

Altmann K-H, Dean NM, Fabbro D, et al. Second generation of antisense oligonucleotides: From nuclease resistance to biological efficacy in animals. CHIMIA Int J Chem 1996; 50: 168-176.

Barts Endocrine 2009. E-Protocols Acromegaly and Growth Hormone. http://www.bartsendocrinology.co.uk/resources/ACROMEGALY+AND+GH+PROTOCOLS+$5Bfinal$5D.pdf.

Buller HR, Cohen AT, Davidson B, et al. Idraparinux versus standard therapy for venous thromboembolic disease. N Engl J Med 2007; 357: 1094-1104.

Crooke ST, Baker BF, Kwoh TJ, et al. Integrated safety assessment of 2'-o-methoxyethyl chimeric antisense oligonucleotides in nonhuman primates and healthy human volunteers. Mol Ther 2016; 24: 1771-1782.

Crooke ST, Baker BF, Xia S, et al. Integrated Assessment of the Clinical Performance of GalNAc3-Conjugated 2'-O-Methoxyethyl Chimeric Antisense Oligonucleotides: I. Human Volunteer Experience. Nucleic Acid Ther 2019; 29: 16-32.

Fisker S. Physiology and pathophysiology of growth hormone-binding protein: methodological and clinical aspects. Growth Horm IGF Res 2006; 16: 1-28.

Geary RS, Yu RZ, Watanabe T, et al. Pharmacokinetics of a tumor necrosis factor-alpha phosphorothioate 2'-*O*-(2-methoxyethyl) modified antisense oligonucleotide: comparison across species. Drug Metab Dispos 2003; 31: 1419-1428.

Giustina A, Barkan A, Beckers A, et al. A Consensus on the Diagnosis and Treatment of Acromegaly Comorbidities: An Update. J Clin Endocrinol Metab 2020; 105:

Henry S, Stecker K, Brooks D, et al. Chemically modified oligonucleotides exhibit decreased immune stimulation in mice. J Pharmacol Exp Ther 2000; 292: 468-479.

Inoue H, Hayase Y, Iwai S, et al. Sequence-dependent hydrolysis of RNA using modified oligonucleotide splints and RNase H. FEBS Lett 1987; 215: 327-330.

Katznelson L, Atkinson JL, Cook DM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly--2011 update. Endocr Pract 2011; 17 Suppl 4: 1-44.

Katznelson L, Laws ER, Jr., Melmed S, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014; 99: 3933-3951.

Kwoh J. 2008 Chapter 13: An Overview of the Clinical Safety Experience of First- and Second-Generation Antisense Oligonucleotides. in S. T. Crooke (ed.), Antisense Drug Technology: Principles, Strategies, and Applications (Boca Raton).

Liu JL, Yakar S, and LeRoith D. Conditional knockout of mouse insulin-like growth factor-1 gene using the Cre/loxP system. Proc Soc Exp Biol Med 2000; 223: 344-351.

McKay RA, Miraglia LJ, Cummins LL, et al. Characterization of a potent and specific class of antisense oligonucleotide inhibitor of human protein kinase C-α expression. J Biol Chem 1999; 274: 1715-1722.

Melmed S. Medical progress: Acromegaly. N Engl J Med 2006; 355: 2558-2573.

Monia BP, Lesnik EA, Gonzalez C, et al. Evaluation of 2'-modified oligonucleotides containing 2'-deoxy gaps as antisense inhibitors of gene expression. J Biol Chem 1993; 268: 14514-14522.

Prakash TP, Graham MJ, Yu J, et al. Targeted delivery of antisense oligonucleotides to hepatocytes using triantennary *N*-acetyl galactosamine improves potency 10-fold in mice. Nucleic Acids Res 2014; 42: 8796-8807.

Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010; 115: 168-186.

Rowland JE, Lichanska AM, Kerr LM, et al. In vivo analysis of growth hormone receptor signaling domains and their associated transcripts. Mol Cell Biol 2005; 25: 66-77.

Schulman S and Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3: 692-694.

Stockert RJ. The asialoglycoprotein receptor: relationships between structure, function, and expression. Physiol Rev 1995; 75: 591-609.

Trainer PJ, Newell-Price JDC, Ayuk J, et al. A randomised, open-label, parallel group phase 2 study of antisense oligonucleotide therapy in acromegaly. Eur J Endocrinol 2018; 179: 97-108.

Tritos NA, Chanson P, Jimenez C, et al. Effectiveness of first-line pegvisomant monotherapy in acromegaly: an ACROSTUDY analysis. Eur J Endocrinol 2017; 176: 213-220.

van der Lely AJ, Biller BM, Brue T, et al. Long-term safety of pegvisomant in patients with acromegaly: comprehensive review of 1288 subjects in ACROSTUDY. J Clin Endocrinol Metab 2012; 97: 1589-1597.

Wang Y, Yu RZ, Henry S, et al. Pharmacokinetics and Clinical Pharmacology Considerations of GalNAc3-Conjugated Antisense Oligonucleotides. Expert Opin Drug Metab Toxicol 2019; 15: 475-485.

Webb SM, Prieto L, Badia X, et al. Acromegaly Quality of Life Questionnaire (ACROQOL) a new health-related quality of life questionnaire for patients with acromegaly: development and psychometric properties. Clin Endocrinol (Oxf) 2002; 57: 251-258.

14. APPENDICES

APPENDIX A. SCHEDULE OF PROCEDURES

Appendix A. Schedule of Procedures – Treatment Period

Study Period	**Screen[1]**	**Treatment Period[2]**																							
Study Week	**-6 to -1**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**21**	**25**	**27**	**29**	**33**	**37**	**41**	**45**	**49**	**53**	**57**	**61**	**65**	**69**	**73**
Study Day	**-42 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**183**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**477**	**505**
Visit Window ± Day	**0**		**3**	**5**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Home Health Care Visit Option[16]					**X**		**X**		**X**		**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	
Informed Consent	X																								
Inclusion/Exclusion	X																								
Medical History	X																								
Disease History	X																								
MRI/CT of sellar	X[3]																			X[3]					X[3]
Echocardiogram	X[3]																								X[3]
AcroQoL		X				X				X			X				X				X				X
ASTS-M		X				X				X			X				X				X				X
EQ-5D		X				X				X			X				X				X				X
SF-36		X				X				X			X				X				X				X
Ring Size Measurement	X	X				X				X			X				X				X				X
Body Weight and Height[4]	X	X		X		X		X		X			X				X				X				X
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam[6]	X	X		X		X		X		X			X				X				X				X
ECG (12-Lead)	X	X		X		X		X		X			X				X				X				X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV, Hepatitis B & C	X																								

Appendix A. Schedule of Procedures – Treatment Period Continued

Study Period	**Screen[1]**	**Treatment Period[2]**																							
Study Week	**-6 to -1**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**21**	**25**	**27**	**29**	**33**	**37**	**41**	**45**	**49**	**53**	**57**	**61**	**65**	**69**	**73**
Study Day	**-42 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**183**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**477**	**505**
Visit Window ± Day	**0**		**3**	**5**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Home Health Care Visit Option[16]					**X**		**X**		**X**		**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	
Screening FSH[7]	X																								
Pregnancy Test[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry Panel (Fasting)[8, 9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Partial PD Panel: GH, IGF-1, GHBP[8]			X		X		X		X		X	X		X	X		X	X		X	X		X	X	
Full PD Panel[8]	X	X		X		X		X		X			X			X			X			X			X
hs-CRP		X	X	X									X						X						X
Coagulation Panel	X	X		X		X		X			X		X						X						X
Pituitary Axis[10], Thyroid Panel	X	X				X							X						X						X
Bone Biomarker		X				X							X						X						X
Lipid panel[8]	X	X				X							X						X						X
Cardiac Biomarkers		X				X							X						X						X
Screening HbA1c	X																								
Glycemic Panel (Including HbA1c)[8]		X				X							X						X						X
2 hr. OGTT and GH Response Assessment[11, 12]		X											X												X
Archived Serum Sample[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix A. Schedule of Procedures – Treatment Period Continued

Study Period	**Screen[1]**	**Treatment Period[2]**																							
Study Week	**-6 to -1**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**	**21**	**25**	**27**	**29**	**33**	**37**	**41**	**45**	**49**	**53**	**57**	**61**	**65**	**69**	**73**
Study Day	**-42 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	**183**	**197**	**225**	**253**	**281**	**309**	**337**	**365**	**393**	**421**	**449**	**477**	**505**
Visit Window ± Day	**0**		**3**	**5**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Home Health Care Visit Option[16]					**X**		**X**		**X**		**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**		**X**	**X**	**X**	
Immunogenicity Testing[14]		X		X		X		X		X			X			X			X			X			X
PK Blood Sampling[14]		X[15]	X	X		X		X		X[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ISIS 766720Administration		X	X	X		X		X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Contact		If a visit cannot be conducted, patient contact (e.g., phone, text, email or video) is required by site personnel to assess Adverse Events and Concomitant Medications																							

ALL STUDY PROCEDURES ARE CONDUCTED PRIOR TO THE ISIS 766720 INJECTION, EXCEPT PK DAY 1 & DAY 113.

1 During the Screening Period, screening results may be retested using the Home Health Care Visit Option for assessment after discussion with the Sponsor Medical Monitor or Designee for eligibility purposes

2 If a patient terminates early from the Treatment Period, an early termination visit from treatment (ETTX) is required as soon as possible, preferably 4 weeks after the last dose. After ETTX visit, patient should continue in Post-Treatment Period, following the schedule in intervals relative to patient's last dose

3 Prior MRI/CT and/or echocardiogram (ECHO) performed within the last 3 months of screening visit can be used. The window to conduct the MRI at Day 365 (WK53) and Day 505 (WK 73) and ECHO at Day 505 (Week 73) is ± 2 weeks

4 Height collected at Screening only

5 BP, heart rate (HR), RR, temperature

6 Full PE to be given at Screening and abbreviated physical exam to be given during Treatment as indicated to assess changes from Screening

7 A pregnancy test is required at Screening for all female patients who are of childbearing potential regardless of age. Serum at Screening, and dipstick is acceptable after Screening. FSH is required to confirm menopause for women ≤ 55 years who have 12 months of spontaneous amenorrhea with no alternative medical cause, and who are not surgically sterile. For patients requiring confirmation of menopause at Screening per protocol, a pregnancy test and FSH are required at Screening, however, once menopause status is confirmed, a pregnancy test is not required in subsequent visits. If patient is surgically sterile, no pregnancy test or FSH is required

8 Fasting is not required at Screening Visit. For all other visits, fasted samples should be taken after fasting for 8 hours. During this time the patient can drink water and they should ensure that they consume enough water to not become dehydrated

9 If the platelet value, serum creatinine or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) or missing, the test must be repeated and a result not meeting stopping rule must be obtained prior to next dose. Platelets require a valid result from the prior platelet test within 21 days up to week 17 and within 35 days after week 17 (per Section 8.5.2). In consultation with the medical monitor or designee, a local lab and central lab should be drawn and evaluated prior to dosing (per Section 6.2.1)

10 A morning cortisol sample is required, and the sample should be drawn prior to 9:00 AM. For patients on stable glucocorticoid therapy, the cortisol sample may be taken at any time

11 Patient should fast for 10 hours prior to OGTT. OGTT Sample Time Schedule: 0, 30, 60, 90, 120 mins. After the 120-min blood draw, the fasting period is completed. See Section 6.2.2 procedure details

Appendix A. Schedule of Procedures – Treatment Period Continued

Legend Continued

[12] The pre-dose Day 1 OGTT may by conducted during the Screening Period between Day -41 and pre-dose Day 1. To decrease the study burden on potential patients, it is suggested that this procedure is done after the patient has completed and qualified for all other screening procedures. The procedure can be conducted in the clinic or by a Home Health Care professional. The window for completing Day 183 and Day 505 OGTT is ± 30 days

[13] Stored at -70 (± 10) °C for follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.)

[14] Unless otherwise specified, all PK and immunogenicity samples must be collected pre-dose

[15] Pre-dose, 1, 2, 4 hours. See Appendix C

[16] Home health may be used at these visits if applicable. In consultation with the Sponsor, a Home Health Care visit may be conducted for a study day visit that was intended to be a clinic visit; it is preferable that the entire visit is conducted, however the following assessments may be omitted: ECG, body weight, physical exam, ring size, and OGTT. Any assessments not completed at the Home Health Care visit should be attempted at the next clinic visit. A confirmation of ISIS 766720 dosing by the Home Health Provider should be obtained and documented in source within 48 hrs

Appendix A. Schedule of Procedures – Post-Treatment Period

Study Period	**Post-Treatment Period (14 Weeks)**				
Study Week (Wk) from Last Dose	**PTWk5**	**PTWk9**	**PTWk15**	**ETTX[1, 2]**	**ETPT[1, 2]**
Study Day from Last Dose	**PTD29[2]**	**PTD57[2]**	**PTD99[2]**	**NA**	**NA**
Study Day from Day 1	**533**	**561**	**604**	**NA**	**NA**
Visit Window ±	**7**	**7**	**7**	**NA**	**NA**
Home Health Care Visit Option[3]	**X**	**X**			
MRI/CT of sellar				X[13]	
Echocardiogram				X[14]	
AcroQoL			X	X	X
ASTS-M			X	X	X
EQ-5D			X	X	X
SF-36			X	X	X
Ring Size Measurement			X	X	X
Body Weight			X	X	X
Vital Signs[4]	X	X	X	X	X
Physical Exam[5]			X	X	X
ECG (12-Lead)			X	X	X
Adverse Events	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
Pregnancy Test[6]	X	X	X	X	X
Chemistry Panel (Fasting)[7, 8]	X	X	X	X	X
Hematology[8]	X	X	X	X	X
Partial PD Panel: GH, IGF-1, GHBP[7]	X	X			
Full PD Panel[7]			X	X	X

Appendix A. Schedule of Procedures – Post-Treatment Period Continued

Study Period	**Post-Treatment Period (14 Weeks)**				
Study Week (Wk) from Last Dose	**PTWk5**	**PTWk9**	**PTWk15**	**ETTX[1, 2]**	**ETPT[1, 2]**
Study Day from Last Dose	**PTD29[2]**	**PTD57[2]**	**PTD99[2]**	**NA**	**NA**
Study Day from Day 1	**533**	**561**	**604**	**NA**	**NA**
Visit Window ±	**7**	**7**	**7**	**NA**	**NA**
Home Health Care Visit Option[3]	**X**	**X**			
hs-CRP			X	X	
Coagulation Panel			X	X	X
Pituitary Axis[9], Thyroid panel and Bone Biomarker, Cardiac Biomarker			X	X	X
Lipid panel[7]			X	X	X
Glycemic Panel[7]			X	X	
2 hr. OGTT and GH response Assessment[10]				X[11]	
Archived Serum Sample[12]	X	X	X	X	X
Immunogenicity Testing	X	X	X	X	X
PK Blood Sampling	X	X	X	X	X
Urinalysis	X	X	X	X	X
Patient Contact	If a visit cannot be conducted, patient contact (e.g., phone, text, email or video) is required by site personnel to assess Adverse Events and Concomitant Medications				

1 The PTWK5 visit does not need to be completed if the ETTX is completed 4 weeks after the last dose. After ETTX visit, patient should continue in Post-Treatment Period, following the schedule in intervals relative to patient's last dose.
2 A Patient terminating from the Post-Treatment Period should complete the ETPT
3 Home health may be used at these visits if applicable for the participating site/country
4 BP, heart rate (HR), RR, temperature
5 Abbreviated physical exam to be given during Post-Treatment Period
6 Dipstick pregnancy test acceptable. If surgically sterile or menopause confirmed at Screening, a pregnancy test is not required in subsequent visits

Appendix A. Schedule of Procedures – Post-Treatment Period Continued

Legend Continued

[7] Fasted samples should be taken after fasting for 8 hours. During this time the patient can drink water and they should ensure that they consume sufficient water to not become dehydrated

[8] If the platelet value, serum creatinine or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis or quantity not sufficient) the test must be repeated. In consultation with the Sponsor Medical Monitor or designee, a local lab and central lab should be drawn and evaluated (per Section 6.2.1)

[9] A morning cortisol sample is required, and the sample should be drawn prior to 9:00 AM. Not required for patients on stable glucocorticoid therapy

[10] Patient should fast for 10 hours prior to OGTT. OGTT Sample Time Schedule: 0, 30, 60, 90, 120 mins. After the 120-min blood draw, the fasting period is completed. See Section 6.2.2 for complete details of the procedure

[11] ETTX OGTT assessment may be completed in the clinic or by a Home Health Care Professional within ± 14 Days. If the patient had completed an OGTT in within the previous 2 months, then the OGTT does not need to be done

[12] Stored at -70(± 10) °C for follow-up exploration of laboratory findings and/or AEs (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies, etc.)

[13] An MRI should be conducted at ETTX for patients who early terminate from the trial after and including Wk 25 but before Wk 53. If the ETTX visit is after Week 53, a third MRI is not required. The window to conduct the ETTX MRI is ± 2 weeks

[14] An ECHO should be conducted at ETTX for patients who early terminate from the trial after and including Wk 25 but before Wk 73. The window to conduct the ETTX ECHO is ± 2 weeks

APPENDIX B. LIST OF LABORATORY ANALYTES

Appendix B. List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of ISIS 766720 or other similar oligonucleotides.

Clinical Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Cholesterol
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- ALP
- Creatine kinase
- GGT
- Lipase

Pituitary Axis

- Morning Cortisol (before 9:00 AM)
- ACTH
- Prolactin
- SHBG
- Testosterone
- FSH (females only)
- LH

Screening Tests

- HBsAg
- Hepatitis C antibody
- HIV antibody
- Serum βhCG
- FSH (females only)[1]

Coagulation

- aPTT (sec)
- PT (sec)
- INR

PD Panel (*Partial PD Panel)

- IGF-1*[5]
- GH*
- GHBP*
- ALS
- IGFBP3

Glycemic Panel

- HbA1c
- Glucose
- Glycated albumin

OGTT Plasma Assessments

- Glucose
- Insulin
- c-peptide
- GH

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells (WBC)
- WBC Differential (% and absolute)
  - Neutrophils
  - Eosinophils
  - Basophils
  - Lymphocytes
  - Monocytes

Thyroid Panel

- TSH
- Free T4
- Total T3

Bone Biomarkers[4]

- Urinary N-telopeptide crosslink (NTX)
- Bone specific alk phos
- Amino terminal propeptide of Type 1 procollagen (PINP)

Pharmacokinetics[2]

- ISIS 766720 levels in plasma

Immunogenicity[2]
Anti-ISIS 766720 antibodies

Inflammatory

- hs-CRP[4]

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- UPCR
- UACR
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[3]

Lipid Panel

- Total Cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides
- VLDL
- Lp(a)

Cardiac Biomarkers[4]

- Cardiac troponin I
- NT-proBNP

[1] Only to confirm post-menopausal state at Screening, if required

[2] Plasma PK and immunogenicity samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, or to assess other actions of ISIS 766720 with plasma constituents

[3] Will be performed on abnormal findings unless otherwise specified

[4] May be analyzed

[5] IGF-1 results will be available from Week 17 visit and every three months or more frequently per PI judgement in consultation with Sponsor Medical Monitor or Designee

APPENDIX C. PK SAMPLING SCHEDULE

Appendix C. PK Sampling Schedule

Treatment Period

Treatment Period																			
Wk 1	**Wk 3**	**Wk 5**	**Wk 9**	**Wk 13**	**Wk 17**	**Wk 21**	**Wk 25**	**Wk 27**	**Wk 29**	**Wk 33**	**Wk 37**	**Wk 41**	**Wk 45**	**Wk 49**	**Wk 53**	**Wk 76**	**Wk 61**	**Wk 65**	**Wk 69**	**Wk 73**
D 1	**D 15**	**D 29**	**D 57**	**D 85**	**D 113**	**D 141**	**D 169**	**D 183**	**D 197**	**D 225**	**D 253**	**D 281**	**D 309**	**D 337**	**D 365**	**D 393**	**D 421**	**D 449**	**D 477**	**D 505**
Blood: Pre-dose, 1, 2, 4 hr, Post-SC Injection	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose, 1, 2, 4 hr, Post-SC Injection	Blood: Pre-dose	Blood: Pre-dose	Blood: Any-time	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose

Note: If 4-hour PK sampling is not possible a protocol deviation can be entered
Wk = week
D = day

Post-Treatment Period

Post-Treatment Period			**Early Termination from Treatment**	**Early Termination from Post-Treatment**
PTWk5	**PTWk9**	**PTWk15**		
D533	**D561**	**D604**	**ETTX**	**ETPT**
Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime

PTWk = post-treatment week
D = day from Day 1

APPENDIX D. GRADING SCALE FOR ADVERSE EVENTS RELATING TO LABORATORY ABNORMALITIES

Appendix D. Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for AEs relating to lab test abnormalities and AEs at the injection site are based upon the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017. Grading used is determined by Investigator Judgement.

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding
Eosinophils increased[1]	>ULN and >Baseline	-	Steroids Initiated
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 x LLN; if abnormal, ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased**	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1.2 - 1.5; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; monitoring only indicated	>2.5; >2.5 x baseline if on anticoagulation; dose adjustment indicated
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline was abnormal
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline normal >1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased**	>ULN - 1.5 x ULN if baseline normal > 1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
GGT increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia††	Fasting glucose value ≥126 mg/dL (7.0 mmol/L)	Change in daily management to maintain fasting blood glucose <126 mg/dL (7.0 mmol/L); e.g. addition of oral antiglycemic agent; workup for diabetes	Insulin therapy initiated; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 mmol/L; hospitalization indicated
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia‡	≥54 mg/dL - <70 mg/dL ≥3.0 mmol/L - <3.9 mmol/L	<54 mg/dL (3.0 mmol/L) AND no assistance required to actively administer carbohydrates, glucagon, or take other corrective actions	Requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
Hypokalemia	<LLN - 3.0 mmol/L	symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs;	4+ proteinuria; Urinary protein ≥3.5 g/24 hrs;
Children	-	Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective invasive intervention indicated
Adverse Events at the Injection Site			
Adverse events at the injection site**	An event at the injection site (e.g. erythema, tenderness, itching) that is easily tolerated by the subject and does not affect the subject's usual daily activities	- Persistent (>24 hours) pain, phlebitis or edema; OR - Lipodystrophy, hair growth or alopecia, OR - Prolonged (>1 month) hypo/hyperpigmentation	- Ulceration or necrosis; severe tissue damage; operative intervention indicated, OR - Any event at the injection site that is incapacitating

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

††Modified for consistency with ADA "Standards of Medical Care in Diabetes - 2018" Diabetes Care 2018;41(Suppl. 1):S13–S27. https://doi.org/10.2337/dc18-S002

‡Modified for consistency with ADA "Glycemic Targets: Standards of Medical Care in Diabetes - 2018", Diabetes Care 2018;41(Suppl. 1):S55–S64. https://doi.org/10.2337/dc18-S006

**Adapted from the original CTCAE V5.0 scale

Protocol

Version:	1
Version Date:	16 Dec 2021
Title:	766720 CS5 Amendment 3 An Open Label, Randomized, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of IONIS GHR-LRX, an Antisense Inhibitor of the Growth Hormone Receptor, Administered Monthly as Monotherapy in Patients

[redacted]

Statistical Analysis Plan

ISIS 766720-CS5

An Open-Label, Randomized, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor, Administered Monthly as Monotherapy in Patients with Acromegaly

Date: 30 August 2022

Version: 2.0

SIGNATURES

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court, Carlsbad, CA 92010

Compound Name:	766720
Protocol:	766720-CS5
Study Title:	An Open-Label, Randomized, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor, Administered Monthly as Monotherapy in Patients with Acromegaly
Issue Date:	13 December 2021 (Protocol Amendment 3 – ROW) 20 December 2021 (Protocol Amendment 4 – Russia)

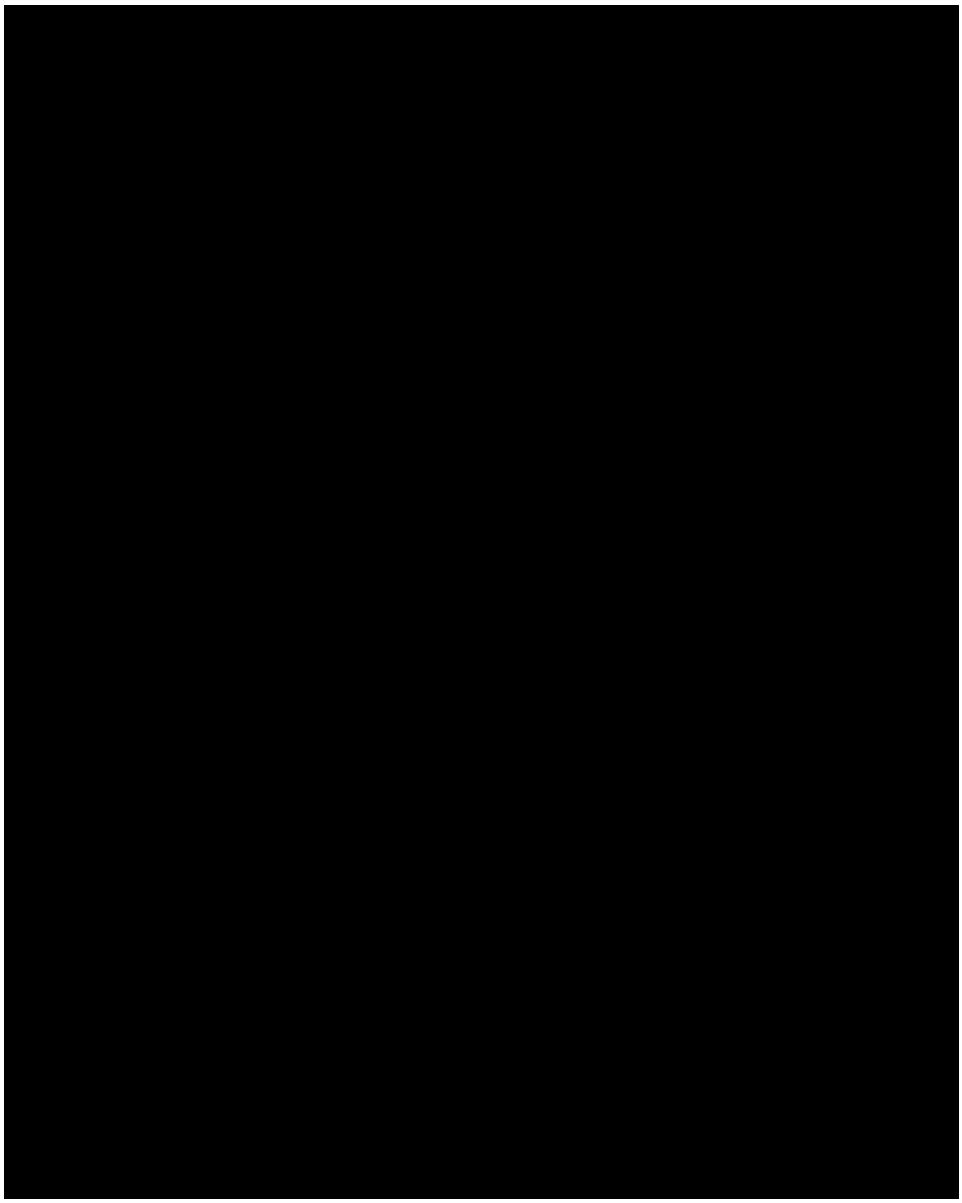


TABLE OF CONTENTS

LIST OF TABLES

SUMMARY OF CHANGES

The following modifications have been made to ISIS 766720 CS5 SAP, Version 2.0, dated 30 August 2022.

List of Modifications

Section	Title	Change/Rationale
Section 3.1	Statistical Design Summary	Updated the patient randomization and clarified enrollment of treatment dose groups per Protocol Amendment 3, dated 13 Dec 2021: [redacted]
Section 3.2.1	Statistical Methods	Updated the baseline definition for IGF-1: Baseline of IGF-1 is defined as the average value of Screening and Day 1 prior to the first administration of ISIS 766720. Multiple results with the same visit label will be averaged first, and baseline IGF-1 will be calculated as IGF-1 at Screening plus IGF-1 at Day 1 divide by 2. Specified additional situations for analytical visits: For patients who had last dose prior to treatment termination, PD results greater than 3 weeks after the last dose (the date of last dose + 21 days) up to treatment termination will not be included in the by-visit summary tables and figures. Also, for patients who started other acromegaly medications in the post-treatment period, PD results after the start date of acromegaly medication will not be included in the by-visit summary tables and figures.
Section 3.3.2 Section 3.4.2 Section 3.5	Analysis of Primary Endpoint Analysis of Secondary Endpoints Exploratory Analyses	Updated the summary groups for efficacy analysis: The results will be summarized by the ISIS 766720 dose received at randomization and overall. In addition, because most of patients will have dose escalation after primary endpoint of Week 27, the results will also be summarized by the maximum ISIS 766720 dose received through the study and overall. Added high-strata and uncontrolled IGF-1 population for PD analysis: 1) IGF-1 > 2.5 × ULN at Screening 2) IGF-1 > 1.3 × ULN at Day 1

Section	Title	Change/Rationale
[redacted]		
Section 3.7	Safety Analyses	Updated the summary groups for safety analysis: The results are summarized by the maximum ISIS 766720 dose received through the study and overall.
Section 3.7.2	Adverse Events	Updated imputation rules for missing dates of adverse events.

ABBREVIATIONS

In addition to the study glossary provided in the protocol, here are additional abbreviations provided for the study SAP.

Abbreviation	Definition
AUC	area under curve
IAUC	incremental AUC

1. INTRODUCTION

This document provides a description of the study organization, study procedures, and the plan for the statistical analysis of the study data. Section 1 discusses study design, objectives, and endpoints; Section 2 provides the study procedures; Section 3 provides the detailed plan for the statistical analyses.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR).

Within this document, the terms 'patient' and 'subject' are both used to describe the individual who enrolls in this study.

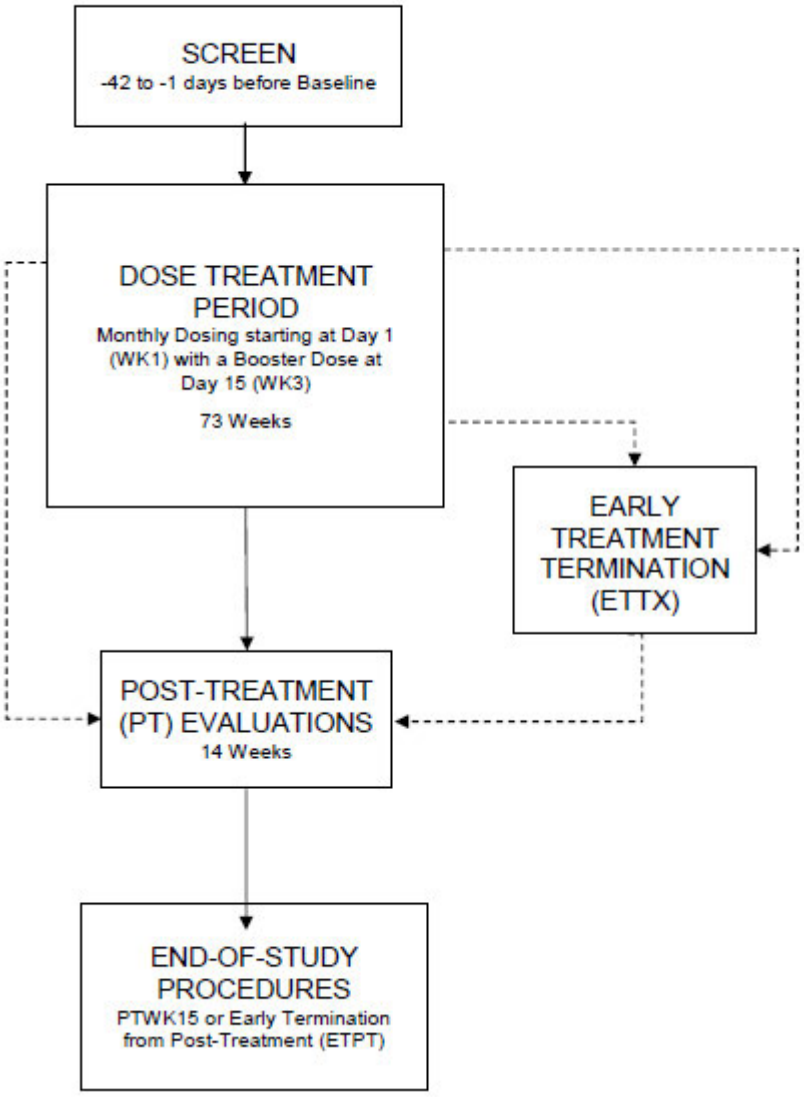
1.1. Study Overview

This is a Phase 2, randomized, open label multi-center study.

All eligible patients will be randomized to one of the 3 treatment groups [redacted] stratified by screening serum IGF-1 level (> 2.5 ULN vs. ≤ 2.5 ULN age and sex adjusted by the central lab). ISIS766720 will be administered as a once monthly SC injection (except during Month 1 where a booster dose is administered on Day 15) during a 73-week Treatment Period). At the end of Treatment Period, patients will enter a 14-week Post-treatment (PT) Evaluation Period.

The Study Design and Treatment Schema are depicted as follows:

STUDY DESIGN AND TREATMENT SCHEMA



1.2. Objectives

1.2.1. Primary Objectives

- To evaluate the safety and tolerability of ISIS 766720 subcutaneous (SC) injection as a monotherapy in patients with acromegaly.
- To evaluate the efficacy of ISIS 766720 SC injection on serum insulin-like growth factor-1 (IGF-1) as a monotherapy in patients with acromegaly.

1.2.2. Secondary Objectives

To evaluate the effect of ISIS 766720 SC to normalize serum IGF-1 levels.

1.3. Endpoints

1.3.1. Primary Endpoint

The primary efficacy endpoint is the percent change in IGF-1 from Baseline to Week 27.

1.3.2. Secondary Endpoints

The following secondary endpoints will be analyzed for efficacy:

- Patients who achieve normalized IGF-1 levels to within 1.2 times gender and age limits at Day 183 (Week 27).
- Patients who achieve normalized IGF-1 levels to within 1.0 times gender and age limits at Day 183 (Week 27).
- Change from Baseline in serum IGF-1 over time.
- Percent change from Baseline in serum IGF-1 over time.

1.3.3. Safety Endpoints

Safety endpoints which will include:

- Adverse events
- Vital signs and weight
- Physical Exams

- Laboratory tests (serum chemistry, hematology, coagulation, urinalysis)
- Echocardiogram
- Electrocardiograms (ECGs)
- Use of concomitant medications

2. PROCEDURES

2.1. General Overview of Procedures

Ionis Pharmaceuticals, Inc. (or designee) will review all study data including source documents, CRFs, and laboratory reports. The study site will enter patient source data into the case report form. Some laboratory data will be transferred electronically from Endocrine Lab, Ludwig-Maximulians-University (LMU) Munich via Medpace Reference Laboratories (MRL), and from Pharmaceutical Product Development (PPD) Inc. (plasma concentration data) to Ionis Pharmaceuticals, Inc.

2.2. Randomization & Treatment Allocation

Patients will be randomized after all screening assessments have been completed and after the Investigator has verified that they are eligible per criteria in protocol Sections 5.1 and 5.2. No subject may begin treatment prior to randomization and assignment of a unique subject identification number.

Eligible patients will be randomized to receive a planned monthly ISIS 766720 SC injection as outlined in protocol Section 3.4.2.

The Sponsor or designee will prepare the randomization list and utilize an automated IRT (Interactive Response Technology) system for randomization assignment.

2.3. Conduct

The study will be conducted in accordance with current Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines, the World Medical Association Declaration of Helsinki guidelines, the Food and Drug Administration (FDA) Code of Federal Regulations, and all other local regulatory requirements.

2.4. Data Monitoring

2.4.1. Safety Data Monitoring

Ionis Pharmaceuticals, Inc. (or designee) is responsible for processing all reported adverse events (AEs). All serious adverse events (SAEs), reported to Ionis Pharmaceuticals, Inc. (or designee), will be reviewed according to standard operating procedures. The medical monitor will review all AEs and SAEs on an ongoing basis throughout the study. Ionis Pharmaceuticals, Inc. (or designee) will prepare and submit safety reports to the health authorities worldwide in accordance with local requirements. If it becomes necessary to communicate new safety information, Ionis Pharmaceuticals, Inc. (or designee) will also prepare a safety notification letter and transmit it to all applicable study sites.

2.5. Data Management

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this Study.

2.5.1. Case Report Form Data

BioClinica, Inc. is responsible for creating the EDC data entry screens, database and edit checks using definitions developed by Ionis Pharmaceuticals, Inc. Ionis Pharmaceuticals, Inc. is responsible for the review, data management querying and locking of the database.

Data are single-entered into the EDC system by the investigator site staff. Programmed edit checks (computer logic that checks the validity of the data entered and also prompts for missing data that is expected to be entered) are run and automatic queries are generated. Ionis Pharmaceuticals, Inc. reviews all data for accuracy and validity and generates additional queries in the EDC system when necessary. The data is corrected or an explanation concerning the query is provided in the EDC system. After all data is entered, source data verified, reviewed

and queried the database is closed. The data is then reviewed by Ionis Pharmaceuticals, Inc. and additional queries may be generated. After all queries are resolved the database is locked.

2.5.2. Laboratory Data

Ionis Pharmaceuticals, Inc. is responsible for the format of the laboratory electronic data transfers, the transfer schedule, and the review of the clinical laboratory data. Investigator sites have access to the data via lab reports sent directly from the laboratory and online using the MRL ClinTrack® database. The laboratory data will be stored as SAS datasets.

2.5.3. Pharmacokinetics (PK) Data

Ionis Pharmaceuticals, Inc. is responsible for the management and review of the plasma ISIS 766720 concentration data from PPD. This review process involves reconciling the patient and visit identifiers (i.e., patient demographics) with the clinical data collected in the EDC system. The final PK data will be stored as CSV and/or EXCEL files. Final data, which has been approved by Quality Assurance, will be stored in the Sponsor's document management system.

3. ANALYTICAL PLAN

3.1. Statistical Design Summary

This is a Phase 2, randomized, open label multi-center study. Approximated 40 eligible patients will be randomized into one of the three treatment groups [redacted]

The primary endpoint is the percent change from Baseline to Week 27 in serum IGF-1 and analyzed by one-sample t-test with an alpha level of 5%. The statistical outcomes are summarized by the ISIS 766720 dose received [redacted] and overall. Additional summary by the adjusted dose (refer to protocol Section 8.7) received may be provided.

An interim analysis may be conducted when approximately 50% of patients complete the primary efficacy assessment. The primary analysis will take place after all patients complete Treatment Period and the database has been locked.

3.2. General Overview of Analyses

3.2.1. Statistical Methods

Descriptive summary statistics including number of patients, mean, median, standard deviation, standard error of mean, 25th percentile, 75th percentile, minimum, and maximum for continuous variables, and counts and percentages for categorical variables will be provided to summarize most data. The study outcomes will be summarized by treatment groups. The efficacy endpoints

will be assessed on the FAS and PPS with the latter being the basis for the primary efficacy analysis. The safety analyses will be performed on the Safety Set. Pharmacokinetic analysis will be conducted in the PK Set.

For the continuous outcomes, the data will be analyzed using one-sample t-test to evaluate the estimate percent changes are different than zero. For the categorical outcomes, the data will be analyzed by using one-sample binomial Exact test (Clopper and Pearson 1934) to evaluate whether the estimate proportions are deviated from zero. The normality assumption for one-sample t-test model will be assessed by the Shapiro-Wilk test. In the case of data departs substantially from normality, the nonparametric Wilcoxon signed rank test will be applied instead. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated. Where appropriate, P-values will also be provided as an indicator to summarize how much deviation from zero within each treatment group based on the statistical tests.

Additional summary of between treatment group comparison may be provided. Treatment group and the stratification factor are included as the independent variables in the statistical model while comparing among treatment groups. For the continuous endpoints, the ANCOVA or ANOVA model will be applied depending on the independent variables or van Elteren test if the data departs substantially from normality. For the dichotomous endpoints, logistic regression will be used instead.

Additional subject listings included case report form (CRF) data and derived outcomes from the data may be presented.

Baseline definition:

Due to the variance of IGF-1 between Screening and Day 1, baseline of IGF-1 is defined as the average value of Screening and Day 1 prior to the first administration of ISIS 766720. Multiple results with the same visit label will be averaged first, and baseline IGF-1 will be calculated as IGF-1 at Screening plus IGF-1 at Day 1 divide by 2.

For other endpoints, baseline is defined as the last non-missing value prior to the first administration of ISIS 766720.

Analytical visits:

In general, all post-baseline data will be summarized using the visit labels provided in the data. Multiple results with the same visit label will be averaged for the continuous variables, and the worst result will be used for the categorical variables. Results with visit labels as “Unscheduled” will not be included in the by-visit summary tables and figures except for determining baseline and the incidence of abnormality lab summary including AST, ALT, platelet and renal but will be presented in data listings.

For patients who had last dose prior to treatment termination, PD results greater than 3 weeks after the last dose (the date of last dose + 21 days) up to treatment termination will not be included in the by-visit summary tables and figures. Also, for patients who started other acromegaly medications in the post-treatment period, PD results after the start date of acromegaly medication will not be included in the by-visit summary tables and figures.

Other situations, such as required additional confirmation, will be described separately in the related endpoint analysis approach.

3.2.2. Subject Population Analyzed

The following analysis populations are defined for this study:

- Safety Set: All patients who are randomized and received at least 1 dose of ISIS 766720.
- Full Analysis Set (FAS): All randomized patients who received at least 1 dose of ISIS 766720- and have at least 1 post-baseline efficacy or PD assessment.
- Per Protocol Set (PPS): All FAS patients who complete at least 6 of the 8 doses of ISIS 766720 within the first 27 weeks administered and have no significant protocol deviations that would be expected to impact efficacy.
- PK Set: All randomized patients who receive at least 1 dose of ISIS 766720 and have at least one evaluable PK sample.

In addition to the above analysis sets, it is recognized that some data displays will be provided for "All Screened", "Screening Failures" and "All Randomized" subjects but no data analysis is planned to be executed in these populations.

Summary of related COVID-19 public health emergency incidence will be described in detail in the corresponding sections.

3.2.3. Handling of Missing Data

Missing values will not be imputed. Patients with missing data for a scheduled assessment time point were excluded from the summary for that time point.

Summary of missing visits for key study parameters will be summarized. Number of patients with missing data and missing data related to COVID-19 public health emergency may be provided.

3.2.4. Disposition of Subjects

The number of patients screened, the number of patients screen failures, the number and percentage of patients enrolled, the number and percentage of patients completed the study treatment, the number and percentage of patients who discontinued from treatment early and reason, the number and percentage of patients completed post-treatment follow-up, and who discontinued from post-treatment follow-up and reason will be summarized.

A by-patient listing will also be provided.

Additional listing will be provided to describe the screen failure, treatment/post-treatment follow-up termination incidences related COVID-19 public health emergency.

3.2.5. Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized using descriptive statistics by safety population. The summary includes age, gender, ethnicity, race, weight, height, and body mass index (BMI). Other disease characteristics related assessments, such as serum IGF-1, will be summarized in the summary tables separately.

For summarizing race, if multiple races are recorded in the database, then 'Multiple Race' is used in the summary table. The listing will display the specific race values.

BMI will be computed using the formula: BMI = (weight in kilograms) / [screening height in cm/100]^2

All protocol deviations will be listed and be summarized. Additional summary table by deviation type and classification will be provided to illustrate the protocol deviations related COVID-19 public health emergency.

3.2.6. Scoring of Questionnaires and Ring Size Assessment

Acromegaly Quality of Life Questionnaire (AcroQoL)

AcroQoL is a specific questionnaire designed to evaluate Health Related Quality of Life (HRQoL) in patients with acromegaly. It comprises 22 items (Table 1), which are spread across 2 dimensions: physical (8 items) and psychological (14 items). There is a further breakdown of the psychological dimension into 2 sub-dimensions (each comprising 7 items): one evaluates appearance and the other evaluates the impact of the disease on the patient's personal relationships.

Table 1: The AcroQoL Questionnaire

	Item
1	My legs are weak*
2	I feel ugly**
3	I get depressed*
4	I look awful in photographs**
5	I avoid going out very much with friends because of my appearance***
6	I try to avoid socializing***
7	I look different in the mirror**
8	I feel rejected by people because of my illness***
9	I have problems carrying out my usual activities*
10	People stare at me because of my appearance***
11	Some part of my body (nose, feet, hands,...) are too big**
12	I have problems doing things with my hands, for example, sewing or handling tools**
13	The illness affects my performance at work or in my usual tasks*
14	My joints ache*
15	I am usually tired*
16	I snore at night**
17	It is hard for me to articulate words due to the size of my tongue**
18	I have problems with sexual relationships***
19	I feel like a sick person*
20	The physical changes produced by my illness govern my life***
21	I have little sexual appetite***
22	I feel weak*

Frequency of occurrence (always, most of the time, sometimes, rarely, never) or degree of agreement with the items (completely agree, moderately agree, neither agree nor disagree, moderately disagree, completely disagree) are the response choices. * Scale 1 (Physical) ** Scale 2-1 (Psychological/ appearance) *** Scale 2-2 Psychological/ personal relations)

AcroQoL dimension	**Questions included in each dimension**
Physical	1, 3, 9, 13, 14, 15, 19, 22
Psychological	2, 4, 5, 6, 7, 8, 10, 11, 12, 16, 17, 18, 20, 21

Sub-dimensions (of the psychological dimension)	**Questions included in each sub-dimension**
Appearance	2, 4, 7, 11, 12, 16, 17
Personal relations	5, 6, 8, 10, 18, 20, 21

Each of the 22 items of the AcroQoL is answered in a 1 to 5 Likert scale measuring either the frequency of occurrence (always, most of the time, sometimes, rarely, or never) or the degree of agreement with the items (completely agree, moderately agree, neither agree nor disagree, moderately disagree, completely disagree). Answers to each of the items are rated on a scale of 1 to 5: 1 corresponds to the response category “Always” or “Completely agree”, depending on the item type, and 5 is equivalent to the response category “Never” or “Completely disagree”. This means that the lower the score the greater the impact on HRQoL.

The scores for each dimension or sub-dimension are the sum of the item responses given for each dimension / sub-dimension. Consequently, the score for the physical dimension can range from 8 to 40 points, the psychological dimension from 14 to 70 points, and each of the sub-dimensions (appearance and personal relationships) from 7 to 35 points. All these scores are interpreted by

taking the lowest score as corresponding to the worst imaginable HRQoL, and the highest score as corresponding to the best imaginable HRQoL, as expressed through the specific scales of this questionnaire. In addition, a global score can be calculated by the sum of the responses to the 22 items, which can range from 22 points (worst HRQoL) to 110 points (best HRQoL).

To simplify interpreting questionnaire scores, the raw scores can be standardized on a scale running from 0 (worst HRQoL) to 100 (best HRQoL), by using the following formula:

$$Y = \left[\frac{(\mathrm{X}) - \min}{(\max - \min)}\right] \times 100$$

Here Y is the re-calculated score, and X is the sum of all the item responses within the dimension or global score (min. is the minimum possible score in the study dimension, and max. is the maximum possible score in the study dimension).

For example, to standardize the global score (Y), substitute X for the sum of the scores of the 22 items, min for 22 and max for 110 (being the two extreme values); thus, scores range from 0 (worst HRQoL) to 100 points (best HRQoL).

$$Global\ score\ Y = \left[\frac{(X)-22}{(110-22)}\right] \times 100$$

To interpret each of the questionnaire scores, all of the items should be answered. However, for most HRQoL questionnaires a score is considered calculable if the percentage of un-answered questions does not exceed 25% of the items used to obtain the score. In such cases, one assumes that the scoring of the missing item or items is equivalent to the average score obtained in the rest of the items that make up the calculation of the score. In the case of AcroQoL, scores can be interpreted for each of the dimensions if the number of unanswered items does not exceed 2 in the physical dimension, 1 in the appearance and personal relationships sub-dimensions, or 3 in the psychological dimension. To get a global score, the maximum number of unanswered questions permissible is 5. The standardized scores of each dimension and global score will be tabulated.

[redacted]

[redacted]

Euro QoL-5 Dimensions (EQ-5D)

The EQ-5D is the most widely used generic PRO instrument internally (Kind 2005) and recommended by NICE for evidence submitted to its technology appraisal process (NICE 2013). The EQ-5D is comprised of 6 questions. The first 5 questions address the following quality of life dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety /depression. The last question is represented by a 20-cm vertical visual analogue scale (VAS), scored from 0 to 100 asking the patient to "mark your own health state today" (Brooks 1996). A new version of the instrument, the five level EQ-5D was developed to improve sensitivity and to standardize the language used across dimensions (Herdman et al. 2011) and the study utilizes this latest instrument.

The EQ-5D comprises the same five questions/dimensions but increases the available response options ('levels') from three to five (no; slight; moderate; severe; extreme problems/unable to).

Short Form 36 (SF-36)

The SF-36 is a multi-purpose health survey with 36 questions and very popular instrument for evaluating health-related quality of life (QoL). The questionnaire measures functional health and well-being from the patient's point of view. The 35 questionnaire are aggregated into eight multi-item health domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH) (based on classification shown in Table 3). The 8 domains, in turn, can be aggregated into two summary domains tapping physical and mental health: a physical component summery (PCS, including PF, RP, GH and BP) and a mental component summary (MCS, including MH, RE, SF, and VT). The SF-36 V2 health Survey form will be used for this study and the norm-based score for each domain will be calculated using Optum's SF36v2/SF-12v2 scoring software. Higher scores are associated with a better QOL. The change and percentage change from Baseline will be tabulated at the scheduled visits.

Table 3: The Abbreviated Item Content for the SF-36 Health Survey Domain Scales

Scale	Item	Abbreviated Item Content
Physical Functioning (PF)	3a	Vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports
	3b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
	3c	Lifting or carrying groceries
	3d	Climbing several flights of stairs
	3e	Climbing one flight of stairs
	3f	Bending, kneeling, or stooping
	3g	Walking more than a mile
	3h	Walking several hundred yards
	3i	Walking one hundred yards
	3j	Bathing or dressing oneself
Role-Physical (RP)	4a	Cut down the amount of time one spent on work or other activities
	4b	Accomplished less than you would like
	4c	Limited in kind of work or other activities
	4d	Had difficulty performing work or other activities (e.g., it took extra effort)
Bodily Pain (BP)	7	Intensity of bodily pain
	8	Extent pain interfered with normal work
General Health (GH)	1	Is your health: excellent, very good, good, fair, poor
	11a	Seem to get sick a little easier than other people
	11b	As healthy as anybody I know
	11c	Expect my health to get worse
	11d	Health is excellent
Vitality (VT)	9a	Feel full of life
	9e	Have a lot of energy
	9g	Feel worn out
	9i	Feel tired
Social Functioning (SF)	6	Extent health problems interfered with normal social activities
	10	Frequency health problems interfered with social activities
Role-Emotional (RE)	5a	Cut down the amount of time spent on work or other activities
	5b	Accomplished less than you would like
	5c	Did work or other activities less carefully than usual
Mental Health (MH)	9b	Been very nervous
	9c	Felt so down in the dumps that nothing could cheer you up
	9d	Felt calm and peaceful
	9f	Felt downhearted and depressed
	9h	Been happy
Reported Health Transition (HT)	2	How health is now compared to 1 year ago

Ring Size Assessment

Per protocol, ring size is assessed using the study provided ring sizer widget and the fourth finger of the non-dominant hand. The ring size to record is the one with the tightest fit. If the finger is too large to be measured by the ring sizer then use the fifth finger (and make a note of this). The same finger will be used throughout the trial. The ring size circumference (mm) will be calculated as:

ring size circumference = ring size *3.14159

Only subjects with post-treatment values using the identical finger as the one used for baseline value will be included in the change and percent change from Baseline analysis.

3.2.7. Stratification, Subsets, and Covariates

Eligible Patients will be stratified on Screening serum IGF-1 level (> 2.5 ULN vs. ≤ 2.5 ULN age and sex adjusted by the central lab).

The following covariates may be used for further exploration in subgroups or as covariates:

- Age group (< 65 years vs. ≥ 65 years)
- Race (Caucasian vs non-Caucasian)
- Gender
- Serum IGF-1 level status (>2.5 ULN vs. ≤ 2.5 ULN)

Additional baseline demographic and disease characteristics may also be considered as covariates.

3.3. Primary Analysis

3.3.1. Primary Endpoint Definition

The primary endpoint is percent change from Baseline to Week 27 in IGF-1 within each ISIS 766720 treated group and overall.

3.3.2. Analysis of Primary Endpoint

The analysis of the study primary endpoint will be conducted in the PPS. The results will be summarized by the ISIS 766720 dose received at randomization and overall. In addition, because most of patients will have dose escalation after primary endpoint of Week 27, the results will also be summarized by the maximum ISIS 766720 dose received through the study and overall.

Subset analysis will be conducted among uncontrolled population (IGF-1 > 1.3 × ULN at Day 1) and high-strata IGF-1 population (IGF-1 > 2.5 × ULN at Screening), separately. The data will be analyzed using one-sample t-test to detect the reduction of IGF-1 significant different than zero at Week 27. The normality assumption for one-sample t-test model will be assessed by the Shapiro-Wilk test. In the case of data departs substantially from normality, the nonparametric Wilcoxon signed rank test will be applied instead. Additional summary in FAS will be provided.

3.3.3. Sample Size Consideration

Approximately 40 patients are planned to be randomized in the study while considering an estimated 10% overall drop-out rate. Based on the assumption of expected IGF-1 reduction of 27.5% from Baseline with SD of 30% per treatment group, the minimum sample size of 12 evaluable patients per treatment group will provide 80% power to detect the difference between the null hypothesis of no change and the expected reduction using a 2-sided one-sample t-test with a significant level of 5%.

3.3.4. Planned Interim Analysis

An interim analysis may be conducted when approximately 50% patients complete the primary efficacy endpoint assessment. Additional summaries may be performed to coincide with study milestones, like publication or regulatory interaction.

3.3.5. Incomplete or Missing Data

In general, missing IGF-1 for a scheduled assessment will not be imputed. Patients with missing data for a scheduled assessment time point will be excluded from the summary for that time point.

3.4. Secondary Analyses

3.4.1. Secondary Endpoint Definitions

Normalized IGF-1 level is defined as the ratio of the serum IGF-1 level and patient's upper limit of normal (ULN). The ULN will be varied among patients due to gender and age. Patients whose calculated ratios at scheduled visits are less than or equal to 1.2 or 1.0 will be deemed as achieving normalized IGH-1 at that scheduled visit.

For change from Baseline, non-missing IGF-1 measures over time will be compared to their baseline.

Patients without IGF-1 measure at a scheduled visit will not be imputed for that scheduled visit.

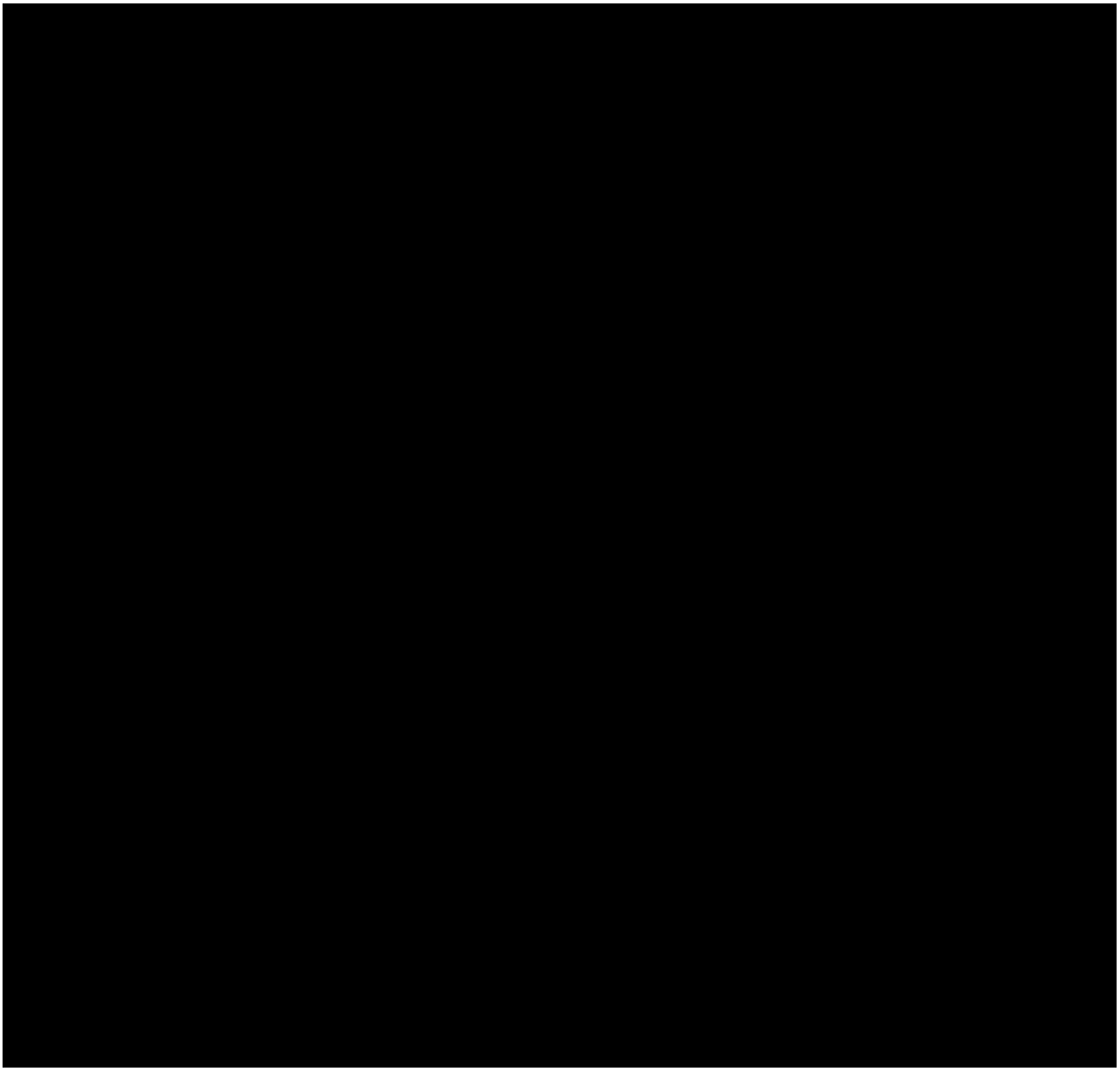
3.4.2. Analysis of Secondary Endpoints

The analysis population will be conducted in both FAS and PPS. The results will be summarized by the ISIS 766720 dose received at randomization and overall. In addition, the results will also be summarized by the maximum ISIS 766720 dose received through the study and overall.

Subset analysis will be conducted among uncontrolled population (IGF-1 > 1.3 × ULN at Day 1) and high-strata IGF-1 population (IGF-1 > 2.5 × ULN at Screening), separately.

Proportion of subject incidence of achieving within 1.2 times, achieving 1.0 times of ULN over time will be summarized at each scheduled visit respectively. The estimated proportion with 95% confidence interval will be provided.

Absolute, change and percent change from Baseline to each scheduled post-baseline visit in IGF-1 over time will be summarized at each scheduled visit.



3.6. Pharmacokinetic Analysis

3.6.1. Plasma Concentration Data of Total Full-Length Oligonucleotides

Pharmacokinetic (PK) analysis will be conducted in the PK Population. For all patients, plasma concentrations of ISIS 766720 (total full-length ASO, reported as ISIS 766720-eq.), along with the scheduled (nominal) and actual samples times (i.e., time from SC dosing) and actual dose will be listed (when applicable) for each patient by dose cohort, nominal dose, patient ID, patient immunogenicity (IM) status, IM onset (if applicable) as defined in Section 3.6.4, and day. In addition, percent differences between scheduled and actual sampling times will be listed for all patients. Percent differences between actual administered dose and nominal dose will also be listed.

Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as "BLQ". For the purpose of calculating descriptive statistics (n, mean, SD, SE, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for plasma concentrations, all BLQ values will be set to zero. Mean plasma concentrations that are BLQ will be presented as BLQ, and the SD, SE, %CV, geometric mean, and geometric %CV will be reported as not applicable. Summary statistics of ISIS 766720-eq. plasma concentrations will be tabulated by nominal dose, nominal day, and scheduled time point.

ISIS 766720-eq. plasma trough (pre-dose) and post-treatment concentration versus time (actual) for each individual patient, as well as the mean (± SD or SE) and/or median plasma trough concentrations over time (scheduled), will be presented graphically on linear and semilogarithmic scales without and with stratification by patient immunogenicity status as applicable (see Section 3.6.4).

At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from the summary descriptive statistics and mean and median plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

3.6.2. Plasma Pharmacokinetic Parameters

Non-compartmental pharmacokinetic analysis of ISIS 766720-eq. will be carried out on each individual patient data set where post-treatment profiles are collected using Phoenix WinNonlin Version 8.0 or higher (Pharsight Corporation, Mountain View, CA). Plasma pharmacokinetic parameters in each patient (when applicable) will be determined. For calculation of PK parameters, all BLQ values will be set to zero. The following plasma PK parameters will be calculated (when applicable and not necessarily limited to) based on actual sampling times:

1. C_{max}: the maximum observed ISIS 766720 concentration in plasma will be determined on Nominal Day 1 and Nominal Day 113.
2. T_{max}: the time at which C_{max} occurs will be determined on Nominal Day 1 and Nominal Day 113.
3. $t_{1/2\lambda z}$: apparent terminal elimination half-life will be calculated from the equation, $t_{1/2\lambda z} = 0.693/\lambda_z$, where λ_z is the rate constant associated with the apparent terminal elimination phase. A minimum of three data points in the elimination phase will be used to define λ_z and the correlation of determination values (r^2 adjusted) has to be at or greater than 0.8 for the estimate to be accepted. This parameter may be calculated following the last dose if applicable.

Plasma pharmacokinetic parameters will be summarized using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) by nominal dose and day.

3.6.3. Pharmacokinetic/Pharmacodynamic Exposure-Response Analysis

Exposure-response correlations may be explored graphically between plasma exposure (i.e., C_{trough}) and selected PD measures (e.g., serum IGF-1, GH, and GHBP levels) if applicable.

Population PK and PKPD analysis may be performed using the PK and PD data from this study and/or combined with other ISIS 766720 clinical PK data later in the development timeline.

3.6.4. Immunogenicity (IM) Analysis

Immunogenicity (IM) analyses will be conducted in the 'Safety Set'. Samples collected for IM assessment at selected time points will be analyzed for anti-ISIS 766720 antibodies (i.e., anti-drug antibodies; ADA). Samples will be designated 'IM positive' based on both positive screening and confirmation assay results (i.e., confirmed positive result), otherwise they will be deemed 'IM negative'. Study subjects will be given 'positive' subject IM status if they have at least one confirmed positive sample at any time during the Treatment or Post-treatment Evaluation Periods. Study subjects will be given 'negative' subject IM status if all evaluated IM sample results during the Treatment and Post-treatment Evaluation Periods are negative and they have at least one evaluable IM result post-dose. Otherwise, study subjects will be given 'unknown' subject IM status.

Sample IM status (screen positive/negative, confirmed positive/negative or not evaluable, and when applicable, titer of anti-ISIS 766720 antibodies) before, during, and after treatment with ISIS 766720 will be listed by the ISIS 766720 dose received (80 mg, 120 mg or 160 mg). Subject IM status (positive/negative or unknown) for all evaluable patients, along with the study day associated with the first positive IM status emerged (T_{first}, i.e., onset of ADA development), the last positive IM status observed (T_{last}) and max and/or end of treatment titer will be listed by treatment and dose.

Additionally, the sample and patient IM incidence (number) and incidence rate (percent) will be summarized as the total number and percent of evaluated patients with antibody negative, positive, and unknown status by the ISIS 766720 dose received (80 mg, 120 mg or 160 mg). Furthermore, onset, and peak titer of the ADA response, if applicable, will be summarized as median, interquartile range (25^{th} percentile, 75^{th} percentile), and range (minimum, maximum).

Other immunogenicity data analysis may be conducted at the discretion of the pharmacokineticist and/or statistician. Potential relationships between immunogenicity results (e.g., IM status) and selected efficacy (e.g., %change in serum IGF-1, GH, and GHBP levels), safety, and pharmacokinetic measures (e.g., C_{trough}) may be evaluated in an exploratory manner either in this report and/or combined with other ISIS 766720 clinical PK data later in the development timeline.

3.7. Safety Analyses

The safety analysis will be conducted on the Safety Set. The results are summarized by the maximum ISIS 766720 dose received through the study and by overall.

3.7.1. Exposure

The time on study will be defined as the total number of days a subject is known to be followed on study calculated as follows:

$$\text{Time on study} = \text{Last date on study} - \text{Date of first dose} + 1,$$

where the last date on study is defined as the date of the latest visit with evaluation for a given subject. Visits with refused or unable to contact are not visits with evaluation

3.7.2. Adverse Events

The incidence of adverse events (AEs) will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 (or higher) preferred term (PT) and system organ class (SOC) for:

- Any treatment emergent adverse events (TEAEs).
- Related TEAEs. Related is defined as "Related", "Possible", or missing relationship to Study Drug.
- Any TEAEs by severity. At each severity level of subject summarization, a subject is classified according to the highest severity if the subject reported one or more events. AEs with missing severity will be categorized as "Missing" for this summary.
- Serious TEAEs.
- TEAEs leading to permanent Study Drug discontinued.

Serious and non-serious AEs that lead to study discontinuation or investigational drug discontinuation will be listed separately. Non-TEAE will be included and be noted in the subject AE listing.

To determine the AE as treatment-emergent or not, if there is no "Formlink" link, and the AE (start date/time) occurs after the subject's first dosing date/time, then the AE is treatment-emergent. Otherwise, if the AE (start date/time) occurs prior to the subject's first dosing date/time, then the AE is not treatment-emergent.

In addition, if there is a "Formlink" link between two AE records, then we compare them pairwise, and consider two cases, where we compare the AE severity (mild/moderate/severe) and seriousness (Yes/No) between the two records in the pair. We chronologically order the 2 records (by AE start date) and refer to the "first" and "second" AE.

Case 1: The first AE record in the pair occurs before first dosing, and the second AE record occurs after first dosing.

If the AE severity or seriousness of the second record is worse than that of the first record, then only the second AE is deemed as a TEAE. Otherwise, neither record is considered as TEAE.

Case 2: Both AE records in the pair occur after first dosing.

Only the worst AE will be deemed as one TEAE.

All TEAEs identified based on the rules above will be summarized in the event number analysis.

Missing Date for Adverse Events

For AEs, the following imputation rules will be applied to impute missing date under conservative principles.

Missing or partial start dates:

If year, month and day are all missing then assign the date of first administration of Study Drug

- If month and day are missing and year is:
  - the same as the year of the first administration of Study Drug then assign the month-day of first Study Drug
  - earlier than the year of the first administration of Study Drug then assign December 31
  - after the year of the first administration of Study Drug then assign January 1
- If only day is missing and month-year is:
  - the same as the month-year of the first administration of Study Drug then assign the day of first Study Drug
  - earlier than the month-year of the first administration of Study Drug then assign the last day of the month
  - after the month-year of the first administration of Study Drug then assign the first day of the month

Imputation will be performed for the end date only if the day or month is missing (i.e., year is present) for a stop date as follows:

- If month and day are missing and year is
  - the same as the year of the last dose of Study Drug then assign the month-day of the last dose of Study Drug
  - otherwise, assign December 31
- If only day is missing then assign the last day of the month

If the imputed start date is later than the imputed end date then set the imputed start date to the imputed end date.

Local Cutaneous Reactions at the Injection Site

Local cutaneous reaction at injection site (LCRIS) is defined as (A) moderate or severe adverse events with the PTs Injection site erythema, Injection site swelling, Injection site pruritus, or Injection site pain that started on the day of injection, persisted for at least two days or ongoing; or (B) any AE at the Study Drug injection site, regardless of severity, that leads to discontinuation of Study Drug, where AE at the Study Drug injection site is the principal reason for discontinuation.

Percentage of injections leading to LCRIS will be calculated as follows for each subject: (A/B)*100, where A = number of injections with an LCRIS, and B = total number of injections. Doses that are split across multiple injections are counted as a single injection.

LCRIS will be summarized using the MedDRA coding system, by SOC/PT. Percentage of the injections leading to LCRIS at injection site will also be summarized.

LCRIS will be listed by preferred term.

Flu-like Reactions

Flu-like reactions are defined as adverse events with PTs including either (A) Influenza like illness or (B) Pyrexia or Feeling hot or Body temperature increased, plus at least two of the following symptoms with the PTs: Chills, Myalgia, or Arthralgia, starting on day of injection or the next day.

Percentage of injections leading to flu-like reactions will be summarized using the descriptive statistics.

Percentage of injections leading to flu-like reactions will be calculated as follows for each subject: (A/B)*100, where A = number of injections leading to flu-like reactions, and B = total number of injections.

FLRs will be summarized using the MedDRA coding system, by SOC/PT. Percentage of the injections leading to FLRs at injection site will also be summarized.

FLRs will be listed by preferred term.

AE of Special Interest (AESI)

Per protocol, severe reductions in platelet count < 50,000/mm^3 accompanied by a clinically relevant bleeding event or platelet count of < 25,000/mm^3 independent of a clinically relevant bleeding event are considered as AESI. The AEs meeting the AESI criteria will be captured in the AE CRF page with a check box to indicate.

AESI will be summarized using the MedDRA coding system, by SOC/PT. A listing of AESI will also be generated.

3.7.3. Vital Signs Measurements

Vital signs will include heart rate, respiratory rate, body temperature, calculated BMI, and systolic and diastolic blood pressure. Vital signs will be summarized for vital sign values as well as the change and percent change from Baseline at each post-baseline visit.

3.7.4. Laboratory Measurements

Bone biomarkers, pituitary axis, thyroid panel, inflammatory, lipid panel, chemistry, hematology, coagulation, cardiac biomarkers and urinalysis (result, change and percent change from Baseline) will be summarized at each post-baseline visit. Listing of laboratory assessments in Chemistry, Hematology and urinalysis will be provided. Local laboratory data will also be provided in the listings separately.

For Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST), the number and percent of subjects falling in each of the following categories will be tabulated:

- ALT/AST > 3 × ULN, confirmed
- ALT/AST > 5 × ULN, confirmed

For Total Bilirubin (BILI), the number and percent of subjects falling in each of the following categories will be tabulated:

- BILI > 1 × ULN, confirmed

A confirmed value is based on a consecutive lab value performed on a different day to, but within 7 days of, the initial value. If the repeated value is in the same or worse category, then the initial value is considered confirmed. If the consecutive value is in a better category, then the initial value is confirmed using the consecutive value category. If values that are not confirmed due to failure to retest or missing lab values, then the initial value is presumed confirmed.

If there are multiple results on the same day (no matter from the same lab vendor or different lab vendors), then the worst value will be utilized in the analysis.

The number and percentage of patients falling in each of the following categories (using available central and local laboratory assessments) based on post-baseline assessments will be provided:

- Confirmed Platelet count 100,000/mm^3 to lower limit of normal (based on central lab)
- Confirmed Platelet count 75,000 to < 100,000/mm^3
- Confirmed Platelet count 50,000 to < 75,000/mm^3
- Confirmed Platelet count 25,000 to < 50,000/mm^3
- Confirmed Platelet count < 25,000/mm^3
- Confirmed ≥ 30% Platelet count decrease from Baseline; further classifying by the lower limit of normal (Above or below)

Additional analysis to explore the possible thrombocytopenia incidence can also be found in AESI described in Section 3.7.1.

Subjects with more than one confirmed value will be counted exactly once under the worst confirmed category.

3.7.5. 12-Lead Electrocardiograms (ECG)

Safety 12 lead ECG will be performed at the visits indicated in the protocol Schedule of Procedures.

The ECG data will include ventricular rate (VR), PR interval, QRS duration, QT, and corrected QT intervals, and overall interpretation.

For the continuous variables above, descriptive statistics (n, mean, standard error, standard deviation, median, 25^{th} percentile, 75^{th} percentile, minimum and maximum) of the results at each study visit, as well as the change and percent change from Baseline to each study visit, will be presented in summary tables; for the categorical responses to overall interpretation, the results at each visit will be summarized by counts and percentages. In addition, patients reported QT interval > 500 msec and QT interval increase more than 60 msec from Baseline will be summarized at each visit. All the ECG data collected will be listed.

3.7.6. Acromegaly Past Medications and Concomitant Medications

Acromegaly Past Medications and concomitant medications will be coded using WHO Drug dictionary (version March 2019) and summarized by ATC class and generic name.

3.7.7. Echocardiograms

Change from Baseline will be summarized for the following parameters, that may include left ventricular mass (LVM), LVM index (LVMi), LV ejection fraction, LV posterior wall thickness (LVPWT), peak velocity ratio (E/A), interventricular septum thickness (IVST) and isovolumic relaxation time (IVRT) whenever possible.

4. REFERENCES

Brooks, R. 1996. "EuroQol: The Current State of Play." *Health Policy* 37: 53–72.

Clopper, C J, and E S Pearson. 1934. "The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial." *Biometrika* 26 (4): 404.

Herdman, M., C. Gudex, A. Lloyd, M. Janssen, P. Kind, D. Parkin, G. Bonsel, and X. Badia. 2011. "Development and Preliminary Testing of the New Five-Level Version of EQ-5D (EQ-5D-5L)." *Qual Life Res* 20: 1727–36.

Kind, Paul. 2005. "EQ-5D Concepts and Methods: A Developmental History," 201–20.

NICE. 2013. "Guide to the Methods of Technology Appraisal 2013."

Version:	1
Version Date:	14 Sep 2022
Title:	766720-CS5 Statistical Analysis Plan V2.0

[redacted]