A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of ISIS 766720 (IONIS-GHR-LRx, an Antisense Inhibitor of the Growth Hormone Receptor) Administered Once Every 28 Days for 16 Weeks in Patients With Acromegaly Being Treated With Long-acting Somatostatin Receptor Ligands (SRL)

NCT03548415

18-May-2020

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Official Title:	**A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of ISIS 766720 (IONIS-GHR-LRx, an Antisense Inhibitor of the Growth Hormone Receptor) Administered Once Every 28 Days for 16 Weeks in Patients With Acromegaly Being Treated With Long-acting Somatostatin Receptor Ligands (SRL)**
NCT Number:	NCT03548415
Document Dates:	Clinical Study Protocol Version 4.0: 18-May-2020

1. STUDY INFORMATION

1.1. Protocol and Protocol Amendments

The protocol was amended 4 times. The latest version of the protocol (Protocol Amendment 4) is provided along with the change summary for the revision.

Protocol Version	Date	Document Provided
Original	25 January 2018	None
Protocol Amendment 1	22 June 2018	None
Protocol Amendment 2	10 August 2018	None
Protocol Amendment 3	14 May 2019	None
Protocol Amendment 4	18 May 2020	Protocol and change summary

IONIS PHARMACEUTICALS, INC.

ISIS 766720-CS2

A Double Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of ISIS 766720 (IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor) Administered Once Every 28 Days for 16 Weeks in Patients with Acromegaly Being Treated with Long-acting Somatostatin Receptor Ligands (SRL)

Protocol Amendment 4 – 18 May 2020

EudraCT No: 2017-004259-22

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ISIS 766720-CS2

Protocol Amendment 4

Licensee Protocol Number 766720-CS2

EudraCT No: 2017-004259-22

Clinical Phase: 2

A Double Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of ISIS 766720 (IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor) Administered Once Every 28 Days for 16 Weeks in Patients with Acromegaly Being Treated with Long-acting Somatostatin Receptor Ligands (SRL)

Protocol History:

Original Protocol:	25 January 2018
Amendment 1:	11 May 2018
Amendment 2:	21 June 2018
Amendment 3	1 May 2019

Sponsor:

Ionis Pharmaceuticals, Inc.
Carlsbad, CA 92010

See electronic signature and date attached at end of document

[redacted] MD, PhD
[redacted]

Confidentiality Statement

This document contains confidential information of Ionis Pharmaceuticals, Inc. that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc

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Protocol Signature Page

Protocol Number:	ISIS 766720-CS2
Protocol Title:	A Double Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of ISIS 766720 (IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor) Administered Once Every 28 Days for 16 Weeks in Patients with Acromegaly Being Treated with Long-acting Somatostatin Receptor Ligands (SRL)
Amendment:	Amendment 4
Date:	18 May 2020

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Double Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of ISIS 766720 (IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor) Administered Once Every 28 Days for 16 Weeks in Patients with Acromegaly Being Treated with Long-acting Somatostatin Receptor Ligands (SRL)," dated 18 May 2020, 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 (E6).

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)

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PROTOCOL AMENDMENT

Protocol Number:	ISIS 766720-CS2
Protocol Title:	A Double Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of ISIS 766720 (IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor) Administered Once Every 28 Days for 16 Weeks in Patients with Acromegaly Being Treated with Long-acting Somatostatin Receptor Ligands (SRL)
Amendment Number:	4
Amendment Date:	18 May 2020

The main purposes of this amendment are to: (1) update several requirements for patient eligibility for the study based on available safety data to date, (2) formalize the procedures added to the protocol based on the guidance given in the May 1, 2020 Memo to Investigators entitled "ISIS 766720-CS2: Coronavirus COVID-19 Guidance – Follow-Up", and (3) update the protocol to reflect the decision to conduct Cohort D.

1. Patient Eligibility Updates:

   a. Three (3) entry criteria have been revised that were originally exclusionary until experience with ISIS 766720 in the acromegaly population was obtained which is now available and includes the acceptable safety profile observed from two ongoing clinical trials including 39 patients from Cohorts A, B, C and D as well as 31 patients in the Open-Label Trial ISIS 766720-CS3 (up to 9 months) to date.

   - The safety data demonstrate a lack of hypoglycemia, therefore, insulin is now permitted at screening and during the study. Exclusion Criteria #19 and #20 have been revised to reflect this. Section 8.10.1 Concomitant Therapy has been updated to reflect this change.
   - The safety data demonstrate no adverse effect on the hypothalamic-pituitary-adrenal axis (HPA) as ACTH and cortisol levels remained within normal limits pre- and post-dosing, therefore, two exclusion criteria have been revised:

     i. A morning blood cortisol level of < 10 mcg/dL was initially considered exclusionary in order to ensure that patients did not have suppression of HPA axis until sufficient data to assess the effects of ISIS 766720 on the HPA axis in acromegaly patients was available. Further, morning cortisol levels are variable and cannot establish the presence or absence of adrenal insufficiency with certainty – for example, many clinicians consider a value of cortisol < 7-8 mcg/dL as indicative of adrenal insufficiency. Most clinicians assess adrenal insufficiency based on cortisol levels coupled with clinical judgement that evaluates signs and symptoms and may use a cosyntropin suppression test (if available). Taken together, Exclusion Criteria #10h has been changed to remove

the specific numeric cut-off value for a morning blood cortisol level of <10 mcg/dL and replaced with the exclusion of a patient if an abnormal morning cortisol test is consistent with symptomatic adrenal insufficiency based on Investigator judgement.

ii. Patients on glucocorticoid replacement therapy are now permitted. Exclusion Criteria #19 has been revised to reflect this. Section 8.10.1 Concomitant Therapy has been updated to reflect this change and specifies that changes in a stable regimen of glucocorticoid replacement therapy may be considered during the study in consultation with the Sponsor Medical Monitor or designee.

b. The protocol contraceptive requirements for male patients has been revised to clarify the requirements for a male patient with a non-pregnant female partner. Inclusion Criteria #5d and Section 6.3.1 Contraception Requirements are revised accordingly.

2. Procedures added based on Memo to Investigators dated May 1, 2020

   The changes will allow for additional visits and procedures to be conducted via home health visits when in-clinic visits are affected due to local precautions and restrictions related to COVID-19 Pandemic (or other circumstances) that may limit the patient's ability to go to the clinic. Specifically, the following has been added to Section 6 Study Procedures and Appendix A Schedule of Procedures:

   - The option to conduct a Home Health Care visit in place of a clinic visit. This can be accommodated in consultation with the Sponsor
   - A Patient Contact Option (e.g., phone, text, email or video) was added to assess adverse events and changes in concomitant medications if a visit cannot be performed

3. Based on the safety and efficacy observed in lower dose levels, the decision to conduct Cohort D was communicated to sites in September 2019. The protocol has been revised to remove the reference that Cohort D "may be conducted" (not included in the list of changes below).

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact the subject safety, exposure, or the overall study design.

A list of changes to the protocol are **BOLDED** and underlined below:

Protocol Section	Description of Change	Rationale
PROTOCOL SYNOPSIS and Section 5 Inclusion Criteria, Section 6.3.1	**Inclusion Criteria** 5d. Males must be surgically sterile, abstinent or, if engaged in sexual relations with a female of child-bearing potential, the patient ~~**or the patient's non-pregnant female partner**~~ must be using 1 highly effective contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 14 weeks after the last dose of Study Drug. 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 informed consent form until 14 weeks after their last dose of study treatment. ~~Male patients engaged in sexual relations with a female of child-bearing potential must also encourage their female partner to use contraception from the time of signing the informed consent until 14 weeks after the patient's last dose of study treatment.~~ **If the male patient's non-pregnant female partner is using a highly effective contraception method, from the time of signing the informed consent form until 14 weeks after their last dose of study treatment, the male patient's contraception requirement is considered fulfilled.**	The update removed the protocol mandated contraception requirement for patient's female partner and added that female partner use of a highly contraceptive method as an alternative option to meet a male patient's contraception requirement.
Synopsis: Study Population Section 5.2 Exclusion Criteria	**Exclusion Criteria** 10h. ~~Morning (prior to 9 AM) blood cortisol < 10 mcg/d: (280 nmol/L)~~ **Abnormal morning cortisol test consistent with symptomatic adrenal insufficiency based on Investigator judgement** 19. Patients may not have ~~**insulin**~~, chronic systemic use of glucocorticoids, weight loss medications or participate in weight loss programs within 2 months before randomization and during study participation. **Patients on glucocorticoid replacement therapy 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.** 20. Patients on anti-diabetes medications must be on a stable dose and regimen for ≥ 3 months prior to screening and throughout the trial. Patients taking GLP-1 agonists **or insulin** can be allowed with prior consultation with the Sponsor Medical Monitor.	See rationale in the Patient Eligibility updates detailed above for changes in Exclusion Criteria

Protocol Section	Description of Change	Rationale
Section 6.1.2 Baseline and Treatment Period Section 6.1.3 Post-Treatment Period	Additional text was added: **In consultation with the Sponsor, a Home Health Care visit may be conducted for a study visit that was intended to be a clinic visit. A confirmation of Study Drug dosing by the Home Health Provider should be obtained and documented in source within 48 hours. It is preferable that the entire visit is conducted, however, the following assessments may be omitted from the Home Health Care visit: ECG, body weight, physical exam, ring size, and OGTT. Any assessments not performed at the Home Health Care visit should be attempted at the next clinic visit.** **If a visit cannot be performed, patient contact (e.g. phone, text or video) is required by site personnel to assess any adverse events or changes in concomitant medications.**	Added to allow flexibility for Home Health Care visits to be conducted to decrease patient burden due to Covid-19 related restrictions or other circumstances that arise during the study that will require Sponsor consultation
Section 6.2.1 Clinical Laboratory Assessments Appendix A Footnote 9	Additional text added: **At any time, the Sponsor Medical Monitor or designee may request both a central and local lab collection in parallel to assess patient safety.**	To reduce patient burden for possible unscheduled visits due to safety follow-up, local lab collections in parallel with central lab collection was added
Section 8.10.1: Concomitant Therapy	Disallowed Concomitant Therapy: The following medications or interventions cannot be started during the trial: other approved or investigational medications for acromegaly (e.g., pasireotide, dopamine agonist or pegvisomant), ~~**insulin**~~, anti-obesity agents or weight loss programs, **and chronic systemic use of** glucocorticoids.	Section updated to allow insulin use as concomitant medication.
Appendix A	A schedule item for **Patient Contact Option** was added: **If a visit cannot be performed, patient contact is required by site personnel to assess Adverse Events and Concomitant Medications** An additional footnote was added: **B 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. These assessments should be attempted at the next clinic visit if not performed at the Home Health Care visit. A confirmation of ISIS 766720 dosing by the Home Health Provider should be obtained and documented in source within 48 hours** **Footnote 20 – removed as Home Health Care is covered in Footnote B now** ~~20. Home Health Care Option can be used for retesting only~~	Added to allow flexibility for Home Health Care visits to be conducted to decrease patient burden due to Covid-19 related restrictions or other circumstances that arise during the study that will require Sponsor consultation

PROTOCOL SYNOPSIS

Protocol Title	A Double Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of ISIS 766720 (IONIS GHR-L_{RX} an Antisense Inhibitor of the Growth Hormone Receptor) Administered Once Every 28 Days for 16 Weeks in Patients with Acromegaly Being Treated with Long-acting Somatostatin Receptor Ligands (SRL)
Study Phase	2
Indication	Acromegaly
Primary Objectives	To evaluate the efficacy of ISIS 766720 subcutaneous injection on serum insulin-like growth factor 1 (IGF-1) vs. placebo as an add-on therapy to long acting somatostatin receptor ligands (SRL) octreotide or lanreotide. To evaluate the safety and tolerability of ISIS 766720 subcutaneous injection vs. placebo on add-on therapy of SRL.
Secondary Objective	To evaluate the effect of ISIS 766720 to normalize serum IGF-1 levels.
Tertiary Objectives	To evaluate the effects of ISIS 766720 subcutaneous injection on growth hormone (GH) over time. To evaluate the effects of ISIS 766720 subcutaneous injection on the following pharmacodynamic endpoints: fasting plasma growth hormone binding protein (GHBP), acid labile subunit (ALS), insulin growth factor binding protein 3 (IGFBP3).
Exploratory Objectives	To evaluate the effects of ISIS 766720 subcutaneous injection on the following glycemic parameters: HbA1c, fasting plasma glucose, glycated albumin as well as glucose, insulin and C-peptide during 2-hour oral glucose tolerance test (OGTT). To evaluate the effects of ISIS 766720 subcutaneous injection on the clinical endpoints using acromegaly quality of life questionnaire (AcroQoL), acromegaly symptoms and treatment score questionnaire (ASTS) and ring size measurement. To evaluate PK exposure over time and potential PK/PD correlation on relevant biomarkers.
Study Design	This is a randomized, double blind, placebo-controlled, multi-center study of ISIS 766720 or placebo as add-on to SRL
Number of Patients	Approximately 60 patients are planned to be randomized in this study. The needed evaluable patients per cohort and their corresponding randomization ratio (ISIS 766720 vs. placebo) are listed as follows: **Cohort** / **Number of Patients** / **Randomization Ratio** A / 15 / 2:1 B / 15 / 2:1 C / 12 / 5:1 D / 12 / 5:1
Study Population	The Sponsor Medical Monitor may be consulted if any questions arise regarding the inclusion or exclusion criteria. **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 documented diagnosis of Acromegaly*. Aged 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 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 for age and sex at time of diagnosis (serum IGF-1 level and MRI at diagnosis will be collected in the CRF).

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	**Inclusion Criteria** ***Continued*** 3. Patients must be on stable maximum or maximally tolerated dose of SRL (lanreotide Autogel or octreotide LAR, per treating physician judgment) every 28 days* for a minimum of 3 months prior to screening and will be required to continue their stable dose of SRL throughout the study. In accordance with US approved prescribing information, the maximal dose recommended per the package insert for lanreotide Autogel is 120 mg every 28 days and for octreotide LAR is 40 mg every 28 days (the reason for the maximally tolerated dose of SRL will be collected in the CRF). SRL dose should not exceed the maximum dose as approved in the local region (as indicated in the SRL label). Prior use of other medications for treating acromegaly (pasireotide, dopamine agonist or pegvisomant) is allowed but not within 6 weeks of screening *Patients who are on a stable monthly dosing regimen, but not exactly every 28 days will be considered for inclusion to this study. Patients who are on a stable regimen, that is not monthly e.g., every 3 weeks or every 6 weeks are excluded. 4. At Screening, serum IGF-1 (performed at central lab) between 1.3 to 5 × ULN, inclusive, adjusted for age and sex 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 FSH levels in the postmenopausal range for the laboratory involved); c. abstinent 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 informed consent form until 14 weeks after the last dose of Study Drug administration Males must be surgically sterile, abstinent or, if engaged in sexual relations with a female of child-bearing potential, the patient must be using 1 highly effective contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 14 weeks after the last dose of Study Drug 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 abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of screening, major non-pituitary surgery within 3 months of screening) or from screening physical examination 2. Patients who received surgery for pituitary adenoma within the last 6 months before the trial, and/or planning to receive surgery during the trial 3. Patients who received radiotherapy for pituitary adenoma within the last 3 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 or CT scan protocol at screening or within 6 months of screening 5. Evidence of decompensated cardiac function per medical judgement and/or 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. Have a diagnosis of Gilbert's disease 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 clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion. (abnormalities may be retested for eligibility purposes) a. Urine protein/creatinine (P/C) ratio ≥ 500 mg/g. In the event of P/C ratio 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. ALT or AST > 1.2 × ULN, bilirubin > ULN; alkaline phosphatase > 3 × ULN d. eGFR < 45 mL/min/1.73m^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 < LLN f. Abnormal thyroid function tests must be approved by the Sponsor Medical Monitor g. HbA1c > 10% h. Abnormal morning cortisol test consistent with 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. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B 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 with a history of other malignancies 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 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 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 a duration ≥ 4 month has elapsed since dosing 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

PROTOCOL SYNOPSIS *Continued*

Study Population ***Continued***	**Exclusion Criteria** ***Continued*** 19. Patients may not have chronic systemic use of glucocorticoids, weight loss medications or participate in weight loss programs within 2 months before randomization and during study participation. Patients on glucocorticoid replacement therapy 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 20. Patients on anti-diabetes medications must be on a stable dose and regimen for ≥ 3 months prior to screening and throughout the trial. Patients taking GLP-1 agonists or insulin can be allowed with prior consultation with the Sponsor Medical Monitor 21. Patients on estrogen containing medications must be on a stable dose and regimen for ≥ 3 months prior to screening and throughout the trial 22. Use of oral anticoagulants, unless the dose has been stable for 4 weeks prior to the first dose of Study Drug and regular clinical monitoring is performed during the trial 23. 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 24. 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
Treatment Groups	There will be up to 4 treatment groups: Cohort A: ISIS 766720 60 mg or placebo (2:1) + SRL every 28 days. In addition, a booster dose of Study Drug is administered on Day 15. Cohort B: ISIS 766720 80 mg or placebo (2:1) + SRL every 28 days. In addition, a booster dose of Study Drug is administered on Day 15. Cohort C: ISIS 766720 120 mg or placebo (5:1) + SRL every 28 days. In addition, a booster dose of Study Drug is administered on Day 15. Cohort D: ISIS 766720 160 mg or placebo (5:1) + SRL every 28 days. In addition, a booster dose of Study Drug is administered on Day 15.
Study Drug Dosage and Administration	ISIS 766720 (100 mg/mL) and placebo will be supplied in vials of 0.8 mL. Study Drug (ISIS 766720 or placebo) injection volumes will be 0.6 and 0.8 mL for Cohort A (60 mg) and Cohort B (80 mg) respectively. For Cohort C the total injection volume will be 1.2 mL (120 mg) and for Cohort D the total injection volume will be 1.6 mL (160 mg). The administration of Study Drug for Cohort C and D may be delivered as a single injection or 2 non-contiguous injections (If 2 non-contiguous injections, volumes such as, 0.6 mL × 2 for 120 mg and 0.8 mL × 2 160 mg, may be used). All Study Drug injections will be subcutaneously administered in the clinic. The patient's stable SRL regimen will continue throughout study participation and ideally administered on the same day as the Study Drug. If the SRL cannot be administered in the Clinic, the administration of SRL relative to Study Drug should be consistent (e.g., 1-3 days after the Study Drug administration during the Treatment Period) throughout the trial. The date and time of each SRL dose will be documented by the patient in a SRL dosing diary and provided to the study center staff at subsequent visits.
Rationale for Dose and Schedule Selection	The dose levels of 60 mg/q28 days and 80 mg/q28 days were selected based on the safety, pharmacokinetic, and pharmacodynamic data from ISIS 766720 Phase 1 study in healthy volunteers. The Phase 1 study evaluated ISIS 766720 doses of 40 mg, 60 mg, and 80 mg administered as single doses and 10 mg, 20 mg and 30 mg administered as 4 doses over a 2-week period that were found to be generally well-tolerated and induced significant reductions in GHBP, a biomarker of GHR inhibition. The safety data obtained in the Phase 1 study (ISIS 766720-CS1) as well as the clinical experience with several other 2′-MOE modified ASOs (Sewell et al. 2002; Chi et al. 2005; Kastelein et al. 2006) and GalNAc conjugated ASOs (Viney et al. 2016; Graham et al. 2017) supports the dosing regimen planned for this Phase 2 study.

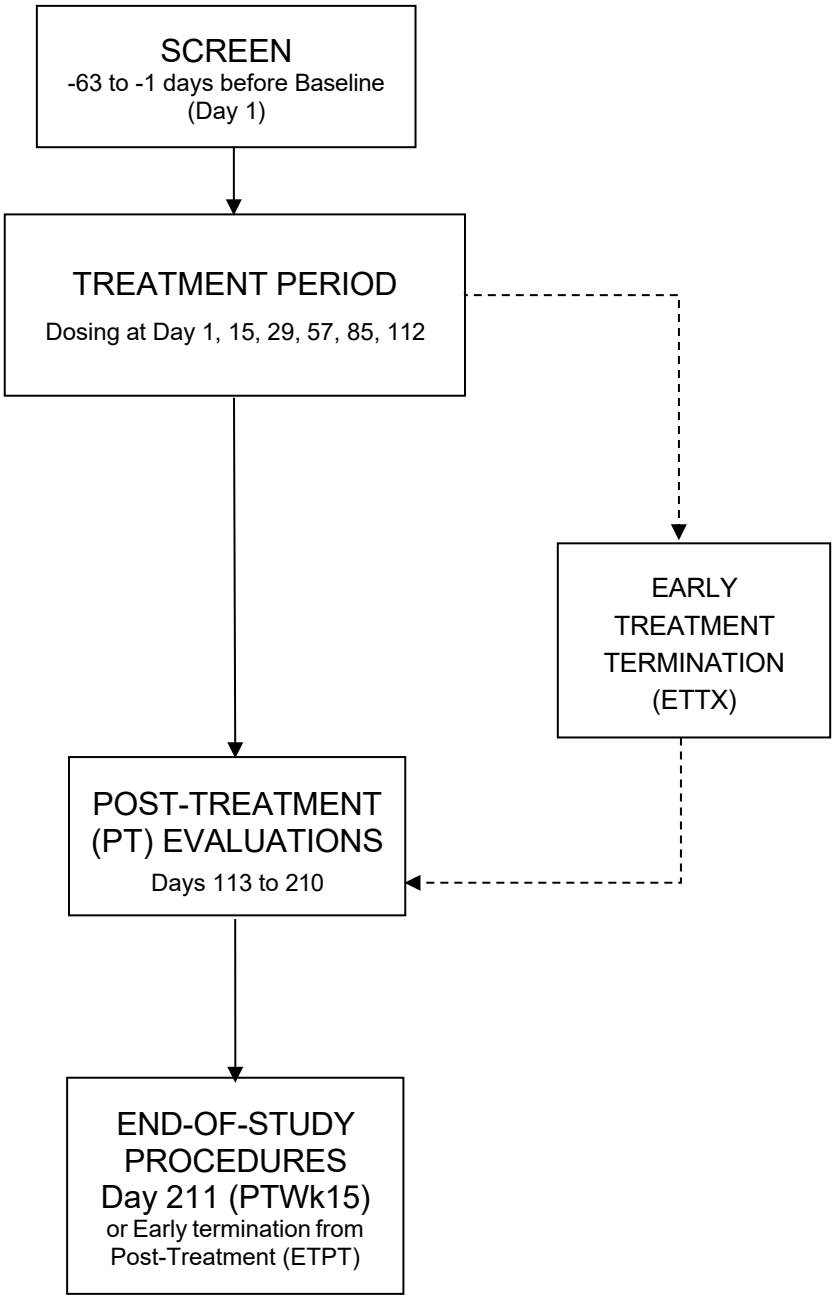
PROTOCOL SYNOPSIS *Continued*

Rationale for Dose and Schedule Selection ***Continued***	The every 28-day dosing regimen (Day 1, 29, 57, 85 and 112) is supported by the long plasma half-life of this compound (approximately 2-3 weeks) and significant GHBP reductions observed after single doses of 60 mg and 80 mg in the Phase 1 study. With every 28-day dosing regimen, steady-state concentrations are expected to be reached approximately after 4-5 doses. Therefore, a booster dose, administered 2 weeks after the first dose (Day 15), is included to achieve steady-state concentrations earlier in the Treatment Period to allow assessment of efficacy with the proposed dosing period (after steady-state concentrations are achieved. The range of dosing proposed for the present study will provide the equivalent drug exposure of 30 mg and 40 mg administered weekly for the first 4 weeks and 15 mg and 20 mg administered weekly for the remaining 12 weeks respectively for Cohort A (60 mg) and Cohort B (80 mg). The highest dose selected for this study, 80 mg every 28 days (e.g., 20 mg per week), is predicted to decrease growth hormone receptor expression aiming for at least 50% reduction in serum IGF-1 levels in acromegaly patients. The dose level of 120 mg/q28 day, and potentially 160 mg/q28 day, have been added to assess the safety and efficacy of higher doses of ISIS 766720. Based on all available data from the nonclinical toxicology program, the no-observed-adverse-effect-level (NOAEL) for ISIS 766720 in the monkey was determined to be 30 mg/kg based on the weekly study for 16 weeks and the monthly dosing regimen study for 9 months. This provides a therapeutic margin of up to 35-fold for an approximate 2.3 mg/kg/month (160 mg/month) clinical dose based on plasma AUC (extrapolated from the Phase 1, 80 mg data). Each patient will receive 6 SC injections of Study Drug in the clinic during the 16-week Treatment Period on Days 1, 15, 29, 57, 85 and 112. The 16-week treatment duration of the trial is supported by the ISIS 766720 nonclinical 16-week toxicology studies (See Investigators Brochure) and by previous long-term weekly clinical dosing studies with several other 2′-MOE-modified ASOs. The SRL dosing regimen will be every 28 days and can be administered in the clinic on Days 1, 29, 57, 85 and 112 during the Treatment Period and will continue monthly during the Post-Treatment Period. If the SRL cannot be administered in the Clinic, the administration of SRL relative to Study Drug should be consistent (e.g., same number of days [1 to 3 days] post Study Drug administration) throughout the trial. The date and time of each SRL dose administered outside of the clinic will be documented by the patient in a SRL dosing diary and provided to the study center staff at subsequent visits.
Study Visit Schedule and Procedures	Detailed information regarding the study procedures is outlined in Section 6, Appendix A, Appendix B, and Appendix C. The study for an individual patient will generally consist of the following periods: • A ≤ 9-week Screening Assessment Period • A 16-week Treatment Period during which Study Drug will be administered as a once-every-28 days SC injection (except during Month 1 where a booster dose is administered on Day 15) • A 14-week Post-Treatment Evaluation Period Once in the Post-Treatment Period, patients who meet eligibility requirements for the open-label extension (OLE) study may elect to enroll in the OLE study and will need to sign the IRB/IEC approved informed consent. Patients not participating in the OLE study will enter the 14-week Post-Treatment Evaluation Period. Laboratory and other study procedures will be performed to assess eligibility during the Screening Periods. Safety and tolerability will be assessed biweekly while efficacy, exploratory and plasma PK assessments will be conducted periodically during the Treatment Period of the study. During the Post-Treatment Period, safety, exploratory and PK will be assessed for 14 weeks. (Schedule of Events in Appendix A and Appendix B). A 2-hour OGTT will be performed (3×) during the study (see Appendix A for details). Assessment of acromegaly clinical symptoms, patient reported outcome, and ring size measurement will be monitored during the Treatment Period and Post-Treatment Period.

PROTOCOL SYNOPSIS *Continued*

Safety and Tolerability Evaluations	The safety and tolerability of ISIS 766720 will be assessed by determining the incidence, severity, dose-relationship of adverse effects and changes in laboratory, ECG, and physical exam evaluations. Safety results in patients dosed with ISIS 766720 will be compared with those from patients dosed with placebo. The safety and tolerability profile of the Study Drug (including liver, renal function, platelet, hypoglycemia and hyperglycemia,) will be monitored regularly during the Treatment Period and at scheduled visits in the Post-Treatment Period.
Efficacy Evaluations	Assessment of the effects of ISIS 766720 on serum IGF-1 percent change from Baseline to 28 days after the last dose (Study Visit PTWk5)
Pharmacokinetic Evaluations	The plasma pharmacokinetics of ISIS 766720 (as total full-length ASO, from fully conjugated to unconjugated ISIS 766720) will be assessed throughout treatment and Post-Treatment Periods. Plasma PK sample collection time points are detailed in Appendix C. Assessment of the effects of ISIS 766720 on serum IGF-1, GH, GHBP, ALS, IGFBP3, as well as glycemic parameters (both fasting and during OGTT) will be measured over time during the Treatment Period and Post-Treatment Period.
Statistical Considerations	Based on prior clinical trial experience with pegvisomant, it is estimated that the standard deviation of the percent change from Baseline serum IGF-1 is approximately 20%. In the Per Protocol Set, with at least 10 planned patients in the pooled placebo group and 10 patients in ISIS 766720 dose group, there will be at least 90% power to detect a 45% difference in mean percent change from Baseline serum IGF-1 between each of the ISIS 766720 dose groups and the pooled placebo group at an alpha level of 0.05. Eligible patients will be stratified based on screening serum IGF-1 levels (> 2.5 × ULN vs. ≤ 2.5 × ULN age and sex adjusted by the central lab). Cohort A and Cohort B are enrolled in parallel and patients will be randomized to 1 of 2 dose cohorts in a 1:1 ratio (Cohort A or Cohort B). Once Cohort A and B enrollment is completed, Cohort C will begin enrollment. Cohort D will be conducted based on the safety and efficacy observed in the lower dose cohorts. Upon randomization to Cohort A or Cohort B patients will be further randomized in a 2:1 ratio to receive either ISIS 766720 or placebo. For Cohort C and Cohort D, the randomization will be in a 5:1 ratio to receive either ISIS 766720 or placebo respectively. An interim analysis may be conducted when at least 6 patients in the higher strata (> 2.5 ×x ULN serum IGF-1) or at least 6 patients in the lower strata (≤ 2.5 × ULN serum IGF-1) complete the Week 11 assessments (2 weeks after Day 57 [i.e., 3 month] dose). Additional interim analysis may also be conducted once each cohort completes the Post-Treatment Week 5 assessments.
Sponsor	Ionis Pharmaceuticals Inc.

STUDY DESIGN AND TREATMENT SCHEMA



STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
AcroQoL	acromegaly quality of life questionnaire
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase (SGOT)
ASTS	acromegaly symptom and treatment score questionnaire
AUC_t	area under the plasma concentration-time curve from time zero to time t
Bb	complement factor Bb (activated complement split product)
βhCG	beta-subunit of human chorionic gonadotropin (pregnancy test)
BP	blood pressure
BUN	blood urea nitrogen
C5a	complement factor C5a (activated complement split product)
C_{max}	maximum concentration
CBC	complete blood count
CMV	cytomegalovirus
CRF	case report form
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
ETPT	early termination visit from post-treatment
ETTX	early termination from treatment
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	good clinical practice
GHBP	growth hormone binding protein
GHR	growth hormone receptor
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
hsCRP	CRP measured by high sensitivity assay

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
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
MPV	mean platelet volume
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
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
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PPS	Per Protocol Set
PT	prothrombin time
QoL	quality of life
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
SAE	serious adverse event
SAP	statistical analysis plan
siRNA	small interfering ribonucleic acid
SC	subcutaneous(ly)
Study Day 1	defined as the first day Study Drug product is administered to the patient
Study Drug	ISIS 766720 or placebo
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
WBC	white blood cell
WOCBP	women of childbearing potential

1. OBJECTIVES

1.1. Primary Objectives

To evaluate the efficacy of ISIS 766720 subcutaneous (SC) injection on serum insulin-like growth factor 1 (serum IGF-1) vs. placebo as an add-on therapy to long acting somatostatin receptor ligands (SRL) octreotide or lanreotide.

To evaluate the safety and tolerability of ISIS 766720 SC injection vs. placebo as add-on therapy to SRL.

1.2. Secondary Objective

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

1.3. Tertiary Objectives

To evaluate the effects of ISIS 766720 SC injection on GH over time.

To evaluate the effects of ISIS 766720 SC injection on the following pharmacodynamic endpoints: fasting plasma GHBP, ALS, IGFBP3.

1.4. Exploratory Objectives

To evaluate the effects of ISIS 766720 SC injection on the following glycemic parameters: HbA1c, fasting plasma glucose, glycated albumin as well as glucose, insulin and C-peptide during 2-hour oral glucose tolerance test.

To evaluate the effects of ISIS 766720 SC injection on the clinical endpoints using AcroQoL, acromegaly sign and symptom treatment score questionnaire (ASTS) and ring size measurement.

To evaluate pharmacokinetic (PK) exposure over time and potential PK/PD correlation on relevant biomarkers.

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 (Melmed 2006). 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).

Surgical removal of the pituitary tumor is the primary treatment for growth hormone 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, 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). 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. 2015).

As a GalNAc conjugated 2′-MOE-gapmer, ISIS 766720 has the potential to be efficacious in treating acromegaly by specifically reducing hepatic expression of GHR and subsequent lowering serum IGF-1 levels. In addition, since mature GHR is cleaved to produce the circulating growth hormone binding protein (GHBP) which binds to circulating GH and prolongs its half-life (Fisker 2006), ISIS 766720 has the potential to decrease circulating GHBP therefore increase GH clearance. Indeed, while preclinical mouse and primate studies with GHR antisense inhibitor demonstrated reduction in hepatic GHR ribonucleic acid (RNA), hepatic GHR protein as well as plasma IGF-1 levels, circulating GH was not increased by ASO treatment unlike comparative mouse studies with Somavert which caused elevations in circulating GH levels. Finally, due to its estimated half-life of 2 to 3 weeks, ISIS 766720 is expected to have a superior duration of action, decreased treatment burden, thereby contributing to the potential of

ISIS 766720 having an enhanced pharmacological benefit and tolerability relative to available acromegaly treatments.

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

2.3.1. Mechanism of Action

ISIS 766720 is an antisense oligonucleotide (ASO) drug targeting GHR RNA. It is covalently bonded to triantennary *N*-acetyl galactosamine (GalNAc), a high-affinity ligand for the hepatocyte-specific asialoglycoprotein receptor (ASGPR) to form an ASO-GalNAc conjugate. This GalNAc-conjugate approach results in enhanced ASO delivery to hepatocytes vs. non-parenchymal cells in the liver and increases ASO potency by ≥ 10-fold in mice (Prakash et al. 2014) compared to unconjugated ASOs. The ASO portion is complementary to base-pair positions 154678-154697 within Intron 2 of the GHR RNA and binds to the RNA by Watson and Crick base pairing. The hybridization (binding) of ISIS 766720 to the cognate RNA results in the ribonuclease H1 (a non-specific endonuclease that catalyzes the cleavage of RNA via a hydrolytic mechanism) (RNase H1)-mediated degradation of the GHR RNA, thus preventing production of GHR protein and its cleavage product GHBP. Since GHBP is in circulation, its level can be used as a biomarker for GHR protein reduction by the ASO.

2.3.2. Chemistry

Chemically, ISIS 766720 is a synthetic oligonucleotide covalently linked to a ligand antisense conjugate (LICA). The oligonucleotide portion of the drug consists of 20 nucleotides (i.e., a 20-mer). Of the nineteen (19) internucleotide linkages, fifteen (15) are 3′-*O* to 5′-*O* phosphorothioate bonds, and 4 are 3′-*O* to 5′-*O* phosphodiesters. The nucleotide sequence of ISIS 766720 is complementary to a 20-nucleotide stretch within Intron 2 of the GHR RNA genomic sequence (NC_000005.10) and binds to the RNA by Watson-Crick base pairing.

Structurally, the oligonucleotide has 4 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (MOE)-modified ribonucleotides, as per Figure 1 below.

These MOE-modified nucleotides confer (1) increased affinity to the target RNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high-dose toxicities thereby resulting in an improved safety profile compared to first generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (DNA) (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 766720 employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1-catalyzed cleavage of RNA hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzyme (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-*O*-(2-methoxyethyl) (2′-MOE) modification to nucleotides

flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition.

A fourth region, comprised of a tri-antennary cluster of *N*-acetyl galactosamine (GalNAc) sugars, is linked to the 5′ end of ISIS 766720 via a phosphodiester linkage. The GalNAc cluster is a high affinity ligand for the asialoglycoprotein receptor (ASGPR), a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The $GalNAc_3$ cluster enhances delivery of ISIS 766720 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the GalNAc cluster is metabolized to release 'free ASO' inside the cell (Prakash et al. 2014). The internucleosidic linkages are a mixture of phosphorothioate and phosphodiester. The phosphorothioate linkages are introduced into the DNA gap region and at both ends of the oligonucleotide to protect it from nuclease mediated metabolism. The mixed backbone design reduces the total number of phosphorothioate linkages which reduces non-specific interactions with proteins and further enhances potency and therapeutic index of GalNAc conjugated ASOs.

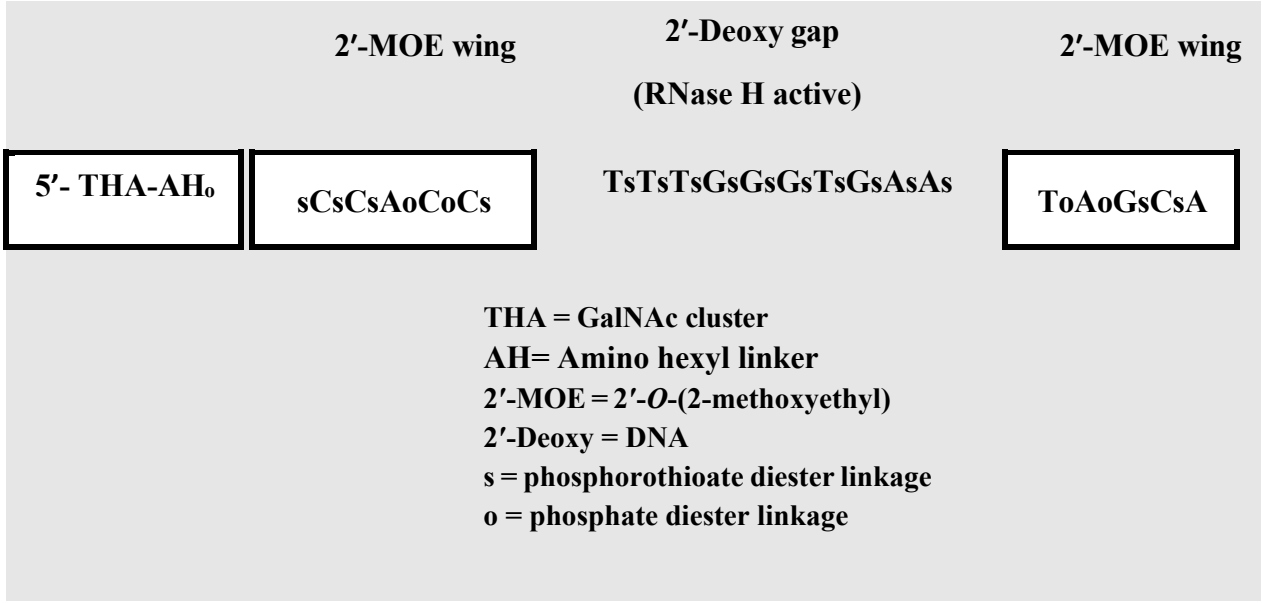


Figure 1 Design of GalNAc Conjugated Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer)

The sequence of ISIS 766720 is shown.

2.3.3. Preclinical Experience

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

The pharmacologic effects of ASOs designed to reduce hepatic GHR messenger ribonucleic acid (mRNA) expression and reduce serum IGF-1 protein expression were examined in mice and in non-human primates. ISIS 766720 exhibits full complementarity to the human and nonhuman primate GHR RNA sequence. ISIS 766720 is pharmacologically active in cynomolgus monkeys, as shown by reductions in hepatic GHR mRNA as well as IGF-1 plasma protein levels with

treatment. The cynomolgus monkey is accepted as a relevant preclinical safety model for oligonucleotide-based therapeutics and the anticipated pharmacologic activity of ISIS 766720 in this species. Since the human GHR transcript is not expressed in rodents, a mouse-specific inhibitor of GHR RNA expression (ISIS 807403) was included in the mouse 16-week and 6-month repeat-dose studies to evaluate the potential effects associated with exaggerated pharmacology in mice.

General repeat-dose toxicology studies were conducted with ISIS 766720 in the mouse and monkey for 6-month and 9-month of treatment, respectively. Pharmacokinetic data confirmed continuous and generally dose-dependent exposure to ISIS 766720. The most noteworthy findings observed in mice and monkeys following ISIS 766720 treatment were, in general, non-specific class effects that are typical for a 2′-MOE ASO. The intended pharmacologic effect of dose-dependent reduction in liver GHR mRNA levels was achieved in both mice and monkeys, with subsequent decreases in serum IGF-1 levels, but there were no toxicologically relevant findings considered to be related to the pharmacologic inhibition of GHR expression in either species.

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.

The safety and tolerability of ISIS 766720 was evaluated in a total of 36 healthy subjects in a double-blinded, placebo-controlled, dose-escalation Phase 1 study ISIS 766720-CS1. Of these 36 subjects, 27 received ISIS 766720 (9 in the single-dose cohorts and 18 in the multiple-dose cohorts), and 9 received placebo. ISIS 766720 was well-tolerated at doses up to 80 mg administered as a single-dose and 120 mg total dose (30 mg administered as 4 doses over 2 weeks). There were no SAEs and all reported AEs were mild in severity. There were no dose-dependent clinically meaningful trends in laboratory assessments.

Since GHBP is a fragment of GHR released into the circulation, reducing GHR expression with ISIS 766720 is expected to lower the circulating GHBP, thus making GHBP a useful biomarker for the activity of ISIS 766720 in healthy volunteers. Indeed, GHBP is decreased in a dose-dependent manner to a mean reduction of approximately 60% observed 15 days after a single-dose of 80 mg ISIS 766720. The effect of ISIS 766720 on IGF-1 will be evaluated in the current study in the relevant patient population.

2.4. Rationale for Dose and Schedule of Administration

The dose levels of 60 mg/q28 days and 80 mg/q28 days were selected based on the safety, PK, and pharmacodynamic data from ISIS 766720 Phase 1 study in healthy volunteers. The Phase 1 study evaluated ISIS 766720 doses of 40 mg, 60 mg, and 80 mg administered as single doses and 10 mg, 20 mg and 30 mg administered as 4 doses over a 2-week period that were found to be generally well-tolerated and induced significant reductions in GHBP, a potential biomarker of GHR inhibition. The safety data obtained in the Phase 1 study (ISIS 766720-CS1) as well as the clinical experience with several other 2′-MOE modified ASOs (Sewell et al. 2002; Chi et al. 2005; Kastelein et al. 2006) and GalNAc-conjugated ASOs (Viney et al. 2016; Graham et al. 2017) supports the dosing regimen planned for this Phase 2 study.

The every 28-day dosing regimen (Days 1, 29, 57, 85 and 112) is supported by the long plasma half-life of this compound (approximately 2-3 weeks) and significant GHBP reductions observed after single doses of 60 mg and 80 mg. With a once-every-28-day dosing regimen, steady-state concentrations are expected to be reached approximately after 4-5 doses. Therefore, a booster dose, administered 2 weeks after the first dose (Day 15), is included to achieve steady-state concentrations earlier in the Treatment Period to allow assessment of efficacy after steady-state concentrations are achieved.

The range of dosing proposed for the present study will provide the equivalent drug exposure of 30 mg and 40 mg administered weekly for the first 4 weeks and 15 mg and 20 mg administered weekly for the remaining 12 weeks; respectively for Cohort A (60 mg) and Cohort B (80 mg). The highest dose selected for this study, 80 mg every 28 days (e.g., 20 mg per week), could decrease hepatic GHR expression resulting in at least a 50% reduction in serum IGF-1 levels in acromegaly patients.

The dose level of 120 mg/q28 day, and potentially 160 mg/q28 day, have been added to assess the safety and efficacy of higher doses of ISIS 766720. Based on all available data from the nonclinical toxicology program, the no-observed-adverse-effect-level (NOAEL) for ISIS 766720 in the monkey was determined to be 30 mg/kg based on the weekly study for 16 weeks and the monthly study for 9 months. This provides a therapeutic margin of up to 35-fold for an approximate 2.3 mg/kg/month (160 mg/month) clinical dose based on plasma AUC (extrapolated from the Phase 1, 80 mg data).

Each patient will receive 6 SC injections in the clinic during the 16-week Treatment Period on Days 1, 15, 29, 57, 85 and 112.

The 16-week treatment duration of the trial is supported by the ISIS 766720 nonclinical 16-week toxicology studies (See Investigators Brochure) and by previous long-term weekly clinical dosing studies with several other 2′-MOE-modified ASOs.

The SRL dosing regimen will be every 28 days and can be administered in the clinic on Days 1, 29, 57, 85, and 112 during the Treatment Period and will continue monthly during the Post-Treatment Period. If the SRL cannot be administered in the Clinic, the administration of SRL relative to Study Drug should be consistent (e.g., same number of days [1-3 days] post-Study Drug administration) throughout the trial. The date and time of each SRL dose administered outside of the clinic will be documented by the patient in a SRL dosing diary and provided to the study center staff at subsequent visits. See Section 6.1.2 for SRL dosing information.

In addition to the experience of ISIS 766720, this dose range is supported by the preclinical and clinical safety experience of several other 2′-MOE-modified ASOs that have been safely administered intravenously and SC in multiple clinical studies at doses up to 1000 mg (Kwoh 2008; Crooke et al. 2016) and for treatment durations that exceed 24 months.

2.5. Risk Assessment

2.5.1. Risk Assessment

Given the short duration of the study, the risks associated with GHR reduction are not anticipated in this trial.

3. EXPERIMENTAL PLAN

3.1. Study Design

This is a double blind, placebo-controlled, Phase 2 study to assess the safety, tolerability, and efficacy of ISIS 766720 administered once every 4 weeks for 16 weeks to patients with acromegaly uncontrolled (IGF-1 level between 1.3 × to 5 × ULN) on select long-acting SRL. Patients will be stratified by the screening IGF-1 level (IGF-1 > 2.5 × ULN or ≤ 2.5 × ULN age and sex adjusted by central lab).

3.2. Number of Study Centers

This study will be conducted at multiple centers worldwide at approximately 40 sites.

3.3. Number of Patients

Approximately 60 patients are planned to be randomized in this study. The number of evaluable patients per cohort and their corresponding randomization ratio (ISIS 766720 vs. Placebo) are listed as follows:

Cohort	Number of Patients	Randomization Ratio
A	15	2:1
B	15	2:1
C	12	5:1
D	12	5:1

3.4. Overall Study Duration and Follow-up

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

- A ≤ 9-week Screening Assessment Period
- A 16-week Treatment Period during which Study Drug will be administered as a once every 4-week SC injection (except during Month 1 where a booster dose is administered on Day 15)
- A 14-week Post-Treatment Evaluation Period

Once in the Post-Treatment Period, patients who meet eligibility requirements for the open-label extension (OLE) study may elect to enroll in the OLE study and will need to sign the IRB/IEC approved informed consent. Patients not participating in the OLE study will enter the 14-week Post-Treatment Evaluation Period.

Patients may be required to attend additional visits for monitoring of adverse events (AE) or abnormal investigation results. The frequency of additional monitoring will be determined by the Study Medical Monitor in consultation with the Investigator.

3.4.1. Screening

Patient eligibility for the study will be determined within 63 days prior to study entry. Sponsor Medical Monitor or designee approval is required for patients to enter the Treatment Period.

3.4.2. Treatment

Eligible patients will report to the Study Center for Study Drug administration per schedule of procedures in Appendix A. Study Drug and SRL will be dosed in clinic every 28 days (in addition, a booster dose of Study Drug is administered on Day 15) while additional visits to collect safety assessments (Day 43, Day 71 and Day 99) could be completed either in clinic or by home health care visit. If the SRL cannot be administered in the Clinic, the administration of SRL relative to Study Drug should be consistent (e.g., same number of days (1 to 3 days) post-Study Drug administration) throughout the trial with date and time documented by the patient in a dosing diary. The treatment duration is 16 weeks. See Section 6.1.2 for timing of SRL dosing.

3.4.3. Post-Treatment

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

3.5. End-of-Study

The End-of-Study is defined as last patient, last visit when all patients complete the last visit of the Post-Treatment Period.

3.6. Data and Safety Monitoring Board

This trial will not have a Data and Safety Monitoring Board.

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, 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 approval by Sponsor Medical Monitor. No patient may begin treatment prior to randomization and assignment of a unique patient identification number.

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 to 1 of 2 dose cohorts in a 1:1 ratio (Cohort A or Cohort B). Within each dose cohort, patients will be further randomized to receive ISIS 766720 or placebo in a 2:1 ratio.

Eligible patients for Cohorts C and D will be stratified based on screening IGF-1 levels (≤ 2.5 × ULN or > 2.5 × ULN, age and sex adjusted by central lab). Patients will be randomized to receive ISIS 766720 or placebo in a 5:1 ratio.

After enrollment in Cohort A and B is completed, Cohort C will begin enrollment. Cohort D will be conducted based on the safety and efficacy results of the lower-dose cohorts

4.3. Replacement of Patients

Patients who withdraw from the study will not be replaced.

4.4. Unblinding of Treatment Assignment

The Sponsor and representatives, and all patients, and Study Center personnel related to the study, will be blinded throughout the study. However, if a patient has suffered a related Serious Adverse Event (SAE) (as defined in Section 9.3.3), and/or when knowledge of the treatment assignment will impact the clinical management of the patient, the Investigator will have the ability to unblind the treatment assignment for that patient using the automated IRT (Interactive Response Technology) system. The Sponsor or designee will be informed of the unblinding of a patient within 24 hours. An unblinded randomization schema will be maintained securely at the Sponsor's designated vendor. In addition, all suspected unexpected serious adverse reactions (SUSARs) will be unblinded by the Sponsor or designee for the purpose of regulatory reporting (see Section 9.2).

Every reasonable attempt should be made to complete the early termination study procedures and observations (see Appendix A and Appendix B) prior to unblinding if needed, as knowledge of the treatment arm could influence patient assessment.

In addition, the Ionis Drug Safety Oversight committee, chaired by the Chief Medical Officer, will also have the ability to request for unblinding the treatment assignment if needed for safety and data interpretation.

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.

The Sponsor Medical Monitor may be consulted if any questions arise regarding the inclusion or exclusion criteria.

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 documented diagnosis of Acromegaly*. Aged 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 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 for age and sex at time of diagnosis (serum IGF-1 level and MRI at diagnosis will be collected in the CRF)
3. Patients must be on stable maximum or maximally tolerated dose of SRL (lanreotide Autogel or octreotide LAR, per treating physician judgment) every 28 days* for a minimum of 3 months prior to screening and will be required to continue their stable dose of SRL throughout the study. In accordance with US approved prescribing information, the maximal dose recommended per the package insert for lanreotide Autogel is 120 mg every 28 days and for octreotide LAR is 40 mg every 28 days (the reason for the maximally tolerated dose of SRL will be collected in the CRF). SRL dose should not exceed the maximum dose as approved in the local region (as indicated in the SRL label). Prior use of other medications for treating acromegaly (pasireotide, dopamine agonist or pegvisomant) is allowed but not within 6 weeks of screening

   * Patients who are on a stable monthly dosing regimen, but not exactly every 28 days will be considered for inclusion to this study. Patients who are on a stable regimen that is not monthly e.g., every 3 weeks or every 6 weeks are excluded.
4. At screening, serum IGF-1 (performed at central lab) between 1.3 to 5 × ULN, inclusive, adjusted for age and sex
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 FSH levels in the postmenopausal range for the laboratory involved)

   c. abstinent 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 informed consent form until 14 weeks after the last dose of Study Drug administration

   Males must be surgically sterile, abstinent or, if engaged in sexual relations with a female of childbearing potential, the patient must be using 1 highly effective contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until 14 weeks after the last dose of Study Drug.

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 abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of screening, major non-pituitary surgery within 3 months of screening) or from screening physical examination
2. Patients who received surgery for pituitary adenoma within the last 6 months before the trial, and/or planning to receive surgery during the trial
3. Patients who received radiotherapy for pituitary adenoma within the last 3 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 or CT scan protocol at screening or within 6 months of screening
5. Evidence of decompensated cardiac function per medical judgement and/or NYHA class 3 or 4
6. Clinical evidence of symptomatic hyperprolactinemia that would necessitate treatment
7. Symptomatic cholelithiasis, and/or choledocholithiasis
8. Have a diagnosis of Gilbert's disease
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 clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion. (abnormalities may be retested for eligibility purposes)

    a. Urine protein/creatinine (P/C) ratio ≥ 500 mg/g. In the event of P/C ratio 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. ALT or AST > 1.2 × ULN, bilirubin > ULN; alkaline phosphatase (ALP) > 3 × ULN

d. eGFR < 45 mL/min/1.73m^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 < LLN

f. Abnormal thyroid function tests must be approved by the Sponsor Medical Monitor

g. HbA1c > 10%

h. Abnormal morning cortisol test consistent with 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. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C or chronic hepatitis B
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 with a history of other malignancies 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
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 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 a duration ≥ 4 month has elapsed since dosing
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 glucocorticoids, weight loss medications or participate in weight loss programs within 2 months before randomization and during study participation. Patients on glucocorticoid replacement therapy 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

20. Patients on anti-diabetes medications must be on a stable dose and regimen for ≥ 3 months prior to screening and throughout the trial. Patients taking GLP-1 agonists or insulin can be allowed with prior consultation Sponsor Medical Monitor
21. Patients on estrogen containing medications must be on a stable dose and regimen for ≥ 3 months prior to screening and throughout the trial
22. Use of oral anticoagulants, unless the dose has been stable for 4 weeks prior to the first dose of Study Drug and regular clinical monitoring is performed during the trial
23. 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
24. 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 9-week Screening Period is provided for completing screening assessments and determining patient eligibility for the study.

During the 9 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 6 months prior to screening. If MRI is contraindicated, then a computed tomography (CT) scan is acceptable.

Individuals may be disqualified if the result of any laboratory test is outside the range specified in the eligibility criteria (Sections 5.1 and 5.2) or, if no range is specified, is abnormal and clinically-significant (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 by the Sponsor Medical Monitor or Designee for eligibility purposes.

The IGF-1 screening (and repeat IGF-1, if needed) blood sample must be drawn up to 3 days prior to or on the day of SRL administration. 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 approval is required for patients to enter the Treatment Period after eligibility is reviewed. Qualified patients will be stratified and randomized and proceed to the Treatment Period Week 1, Day 1 Assessments.

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

6.1.2. Baseline and Treatment Period

All randomized patients will return to the clinic for Study Drug on Day 1, Day 15 (Study Drug administration only), Day 29, Day 57, Day 85 and Day 112. All Study Drug administration occurs at the beginning of a study week with the exception that the last Study Drug administration is conducted at the **END** of the Study Week – Week 16, Day 112. The patient's stable SRL regimen will continue throughout study participation and the administration of SRL relative to Study Drug must be consistent throughout the trial. Therefore, plan to align all SRL injections to be either i) the same day as the Study Drug administration, or ii) up to 3 days after the Study Drug administration. The IGF-1 blood sample must be taken prior to Study Drug administration.

If the SRL cannot be administered in the Clinic, the date and time of each SRL dose will be documented by the patient in a SRL dosing diary and provided to the study center staff at subsequent visits.

Safety, efficacy, PK and exploratory assessments will be performed per Appendix A, Appendix B, and Appendix C throughout the Treatment Period on Study Drug administration days and on Day 43, Day 71 and Day 99. The study procedures required on Day 43, Day 71 and Day 99 may be performed outside the clinic by a Sponsor selected Home Health Care professional. In consultation with the Sponsor, a Home Health Care visit may be conducted for a study visit that was intended to be a clinic visit. A confirmation of Study Drug dosing by the Home Health Provider should be obtained and documented in source within 48 hours. It is preferable that the entire visit is conducted, however, the following assessments may be omitted from the Home Health Care visit: ECG, body weight, physical exam, ring size, and OGTT. Any assessments not performed at the Home Health Care visit should be attempted at the next clinic visit.

If a visit cannot be performed, patient contact (e.g., phone, text or video) is required by site personnel to assess any adverse events or changes in concomitant medications.

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 usage will be assessed during each visit.

A 2-hour Oral Glucose Tolerance Test (OGTT) will be conducted on Study Day 1 pre-dose and Day 57. The Day 1 OGTT can be conducted between Day -7 and Day-1. Acromegaly symptom and treatment score (ASTS) questionnaire and quality of life via AcroQoL questionnaire will be assessed along with ring size assessment periodically throughout the study. See Section 6.2 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 and ring size assessments prior to all other procedures and dosing (see Section 6.2). All blood samples should be drawn prior to Study Drug administration (exceptions are the post-dose samples for PK sampling).

During each visit, the study staff should attempt to complete all the study procedures prior to Study Drug administration as outlined in the Appendix A , however, if a procedure is conducted after Study Drug 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 2 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 16 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 3 Visit (PTWK3) is 14 days after the last dose and 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 analysis, will be performed as indicated in the Appendix A, Appendix B and Appendix C. Patients will continue their SRL therapy, Safety and efficacy data, including any AEs and concomitant medications will be recorded and reviewed by the Sponsor's Medical Monitor or designee. The Investigator after consultation with the Sponsor Medical Monitor or designee may conduct an MRI (or CT when MRI is contraindicated) in the Post-Treatment Period if clinically indicated. A 2-hour OGTT will be conducted at the PTWk5 visit. The AcroQoL, ASTS, and ring size assessment will be conducted periodically in the Post-Treatment Period.

In consultation with the Sponsor, a Home Health Care visit may be conducted for a study 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 from the Home Health Care visit: ECG, body weight, physical exam, ring size, and OGTT. Any assessments not performed at the Home Health Care visit should be attempted at the next clinic visit.

If a visit cannot be performed, patient contact (e.g., phone, text or video) is required by site personnel to assess any adverse events or changes in concomitant medications.

Once in the Post-Treatment Period, patients who meet eligibility requirements for the open-label extension (OLE) study may elect to enroll in the OLE study and will need to sign the IRB/IEC approved informed consent. Patients not participating in the OLE study will enter the 14-week Post-Treatment Evaluation Period.

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

6.2. Study 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 lab. The next dose of Study Drug may not be administered until a result not meeting a stopping rule is available.

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

6.2.2. Oral Glucose Tolerance Test (OGTT)

Patients will undergo 3 OGTT procedures during the Treatment Period (X2) and Post-Treatment Period (X1) per Appendix A. For each OGTT procedure, patients should begin fasting for 10 hours the evening 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 is inserted and a 5-minute period is allowed to remove any effects linked to the stress induced by venipuncture. Blood sampling will begin at Time 0-before the glucose solution is consumed. The glucose 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 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 Study Drug is administered.

Table 1 Sampling Schedule: Day of Oral Glucose Tolerance Test (OGTT)

Intervention	Time (Minutes)	OGTT Sampling
Study Day		**D1*, 57, 141**
	-5	Catheter Insertion (if used)
T_0 = 75 grams Glucose Ingestion	0 Prior to Glucose ingestion	Glucose, Insulin, C-peptide
	30	Glucose, Insulin, C-peptide
	60	Glucose, Insulin, C-peptide
	90	Glucose, Insulin, C-peptide
	120#	Glucose, Insulin, C-peptide

* Day 1 OGTT: The Day 1 OGTT can be conducted between Day-7 and Day-1. The procedure can be conducted in the clinic or as arranged by a Home Health Care professional

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

6.2.3. Assessments for Acromegaly

There are up to 3 procedures that will be conducted that assess signs, symptoms and quality of life (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) Acromegaly Symptoms and Treatment Score Questionnaire (ASTS); 3) Ring Size Assessment. AcroQoL and ASTS will be a paper assessment filled out by patients and the results are entered into eCRF by site staff
3. It may take approximately 20 minutes to complete all 3 assessments

Prior to filling out the AcroQoL and ASTS 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, iii) they should be aware that there are no wrong answers, and iv) it is important to answer all questions.

Note: Deviations from the order of completion or relation of completion to Study Drug administration will not be considered a significant deviation that will impact efficacy.

6.2.3.1. Acromegaly Quality of Life Questionnaire (AcroQoL)

To assess the health-related quality of life 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 (ASTS)

Patients will be asked to complete the assessment to monitor symptoms relating to the 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 Study Drug and effectiveness of SRL). This questionnaire will take about 5 minutes to complete. Patients should leave Question #5 blank for Day 1 and Post-Treatment days 127, 141, 155, 183, 211, and ETPT.

6.2.3.3. Ring Size Assessment

Finger size is an objective measure of soft tissue swelling and over growth 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 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 (Barts Endocrine 2009). If possible, the same study personnel should conduct the ring size assessment at each clinic visit.

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 informed consent form until 14 weeks after their last dose of study treatment.

If the male patient's non-pregnant female partner is using a highly effective contraception method, from the time of signing the informed consent form until 14 weeks after their last dose of study treatment, the male patient's contraception requirement 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:

- Highly effective male contraception includes: a vasectomy with negative semen analysis at Follow-up, sexual abstinence†, non-pregnant female partner uses 1 highly effective contraceptive methods (defined below)
- Male patients with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the Study Drug
- For female partners of male patients, contraception should be encouraged

Female patients of childbearing potential:

- Using 1 highly effective method of contraception: 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.

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.

7. STUDY DRUG

7.1. ISIS 766720 or Placebo

The characteristics of the Study Drug (ISIS 766720 or placebo) are listed in Table 2.

The Study Drug is contained in 2 mL stoppered glass vials. The Study Drug and its storage and preparation instructions will be provided by the Sponsor or Designee. The Study Drug must be stored securely at 2-8 °Celsius and be protected from light.

Table 2 Study Drug Characteristics

Study Drug	ISIS 766720	Placebo
Strength	100 mg/ mL	Not Applicable
Volume/Formulation	0.8 mL solution per vial	0.8 mL solution per vial
Route of Administration	subcutaneous	subcutaneous

7.2. Packaging and Labeling

The Sponsor will provide the Investigator with packaged ISIS 766720 and placebo 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 Study Drug (ISIS 766720 or placebo) supplies provided by the Sponsor according to Sponsor instruction and in accordance with institutional policy.

8. TREATMENT OF PATIENTS

8.1. Study Drug Administration

During Treatment Period, Study Drug will be administered subcutaneously during clinic visits by study nurse or by Home Health professional outside of clinic per schedule of procedure in Appendix A. Study Drug (ISIS 766720 or placebo) injection volumes will be 0.6 and 0.8 mL for Cohort A (60 mg) and Cohort B (80 mg) respectively. For Cohort C the total injection volume will be 1.2 mL (120 mg) and for Cohort D the total injection volume will be 1.6 mL (160 mg).

The administration of Study Drug for Cohort C and D may be delivered as a single injection or 2 non-contiguous injections (If 2 non-contiguous injections, volumes such as, 0.6 mL × 2 for 120 mg and 0.8 mL × 2 for 160 mg may be used).

Please refer to the Study Drug Manual provided by the Sponsor or designee for more detailed instructions for Study Drug (ISIS 766720 or placebo) preparation and administration.

Table 3 Study Drug Dosing Information

Cohort	Volume to Administer	Total Dose
Cohort A	0.6 mL	60 mg or placebo
Cohort B	0.8 mL	80 mg or placebo
Cohort C	1.2 mL	120 mg or placebo
Cohort D	1.6 mL	160 mg or placebo

8.2. Other Protocol-Required Drugs

Patients must be on stable maximum or maximally tolerated dose of SRL (lanreotide Autogel or octreotide LAR every *28 days), for a minimum of 3 months prior to screening and will be required to continue their SRL throughout the study. During study participation, SRL can be administered during clinic visits by the staff with the location of the injection recorded in eCRF.

* Patients who are on a stable monthly dosing regimen, but not exactly every 28 days will be allowed. Patients who are on a stable regimen that is not monthly e.g., every 3 weeks or every 6 weeks are excluded.

8.3. Other Protocol-Required Treatment Procedures

There is 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-dosed 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 3 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 Study Drug (ISIS 766720 or placebo).

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 Study Drug (ISIS 766720 or placebo), 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 x 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 ≤ 1.2 × ULN or 1.2 × 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], hepatitis C virus [HCV] antibody, 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. 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 Adjustments 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 Study Drug 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

If a patient's platelet count falls by 30% or greater from Baseline or the absolute platelet count is 100,000/mm^3 or less, then the patient's platelet counts should be monitored weekly. In case of platelet reduction to below 75,000/mm^3, the platelet monitoring rule defined in Stopping rules (Section 8.6.3) should be followed.

Treatment should be held if there is no evaluable platelet count within the 2 weeks (+7 days) 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.

In the event of a platelet count < 75,000/mm^3, additional laboratory investigations may be conducted in consultation with Medical Monitor (Table 4).

Table 4 Additional Labs to be Performed in the Event of a Platelet Count < 75,000/mm^3

To Be Performed at Local Lab
Peripheral smear (should be performed locally, fixed and sent to central lab for review)
Fibrinogen split products or D-dimer on fresh blood
To Be Performed at Central Lab
Citrated sample for platelets Coagulation panel (PT/INR, activated partial thromboplastin time [aPTT]) CBC (complete blood count) with reticulocytes and mean platelet volume (MPV)
Fibrinogen
von Willebrand factor
Total globulins, total IgA, IgG and IgM
Complement: total C3, total C4, Bb, C5a
CRP measured by high sensitivity assay (hsCRP)
Serology for:
hepatitis B virus (HBV), HCV, HIV (if not done for screening)
Rubella
cytomegalovirus (CMV)
EBV
Parvo B19
Helicobacter pylori (IgG serum test)
Auto-antibody screen:
Antiphospholipid
Rheumatoid factor
Anti-dsDNA
Anti-thyroid
Vitamin B12
Folic Acid
To Be Performed at Specialty Lab(s)
Antiplatelet antibodies and Anti-PF4 assay
Anti-ASO antibody

Note: The above labs may change as additional data is assessed, and sites will be updated regarding any changes

8.5.3. Safety Monitoring for Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (which are defined in Section 8.6.3), for example excess bruising, petechiae, gingival bleeding on brushing teeth. If a minor bleeding event occurs, additional testing of coagulation parameters (aPTT, PT, INR) and platelet count should be performed.

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, Urine protein/creatinine ratio > 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,** dosing of a patient with Study Drug (ISIS 766720 or placebo) 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. 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 Study Drug (ISIS 766720 or placebo) 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 of protocol)
2. Proteinuria, Urine protein/creatinine ratio > 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 Study Drug 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 5).

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 major bleeding or clinically-relevant non-major bleeding (defined below; (Schulman and Kearon 2005; Buller et al. 2007), dosing with Study Drug 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 Study Medical Monitor 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 Study Drug, the platelet count falls below 75,000/mm^3, further dosing of the patient with Study Drug 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 non-major bleeding (CRNMB) is defined as overt bleeding not meeting the criteria for major bleeding 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 major bleeding or clinically-relevant, non-major bleeding events (defined above), for example excess bruising, petechiae, gingival bleeding on brushing teeth.

Table 5 Actions in Patients with Low Platelet Count

Platelet Count on Rx	Drug Dose	Monitoring
> 100,000/mm^3	No action	Monitor every 2 weeks
≥ 75,000 - ≤ 100,000/mm^3	No action	Monitor every week until 3 successive values > 100,000/mm^3
≥ 50,000 - < 75,000/mm^3	Pause dosing When platelet count returns to > 100,000/mm^3 restart dosing **only if approved by Sponsor Medical Monitor**	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 - < 50,000/mm^3	Permanently discontinue Study Drug	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 Study Drug	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

Dose adjustments, including dose interruptions, and/or decreasing the dose will be allowed for safety or tolerability after consultation with the Sponsor Medical Monitor.

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

8.8. Discontinuation of Study Drug

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

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an AE that necessitates permanent discontinuation of Study Drug
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Section 8.6.1 to Section 8.6.3
- The patient experiences an AE that necessitates unblinding of the Investigator or Sponsor to the patient's treatment assignment
- The patient meets any of the following Exclusion Criteria (see Section 5.2) after discussion with the Sponsor Medical Monitor
  - 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/CT protocol

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

Patients who discontinue Study Drug should complete ETTX visit and then enter the Post-Treatment Period) unless consent is withdrawn. Minimally, every effort should be made to complete the early termination study procedures (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 notified to the Sponsor.

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.

Disallowed Concomitant Therapy

The following medications or interventions cannot be started during the trial: other approved or investigational medications for acromegaly (e.g., pasireotide, dopamine agonist or pegvisomant), anti-obesity agents or weight loss programs, and chronic systemic use of glucocorticoids. Changes to a stable regimen of estrogen containing medication or antidiabetic medications allowed at screening may 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 for treatment of glucose lowering effects – 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

Compliance with treatment dosing and SRL dosing is to be monitored and recorded in the eCRF by Study Center staff.

There is not a patient diary for this trial for all patients, but there is a SRL dosing diary for patients who receive SRL administration outside of the clinic.

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 Safety Management Plan 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 SAEs including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. 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 the Study Drug (ISIS 766720 or placebo) 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.

Appropriate personnel at the Sponsor or designee will unblind SUSARs for the purpose of regulatory reporting. The Sponsor or designee will submit SUSARs to Regulatory Agencies in blinded or unblinded fashion according to local law. The Sponsor or designee will submit SUSARs to Investigators in a blinded fashion.

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/Study Drug.

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 Study Drug
- 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 Unexpected Suspected 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 one 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]; 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).

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

9.3.3.1. Adverse Events of Special Interest (AESI)

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

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 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 Study Drug) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's Follow-up Period which is defined as ET15/PT15 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. SAEs should be reported using an Initial Serious Adverse Event Form. The Form should be completed, and a copy faxed or emailed 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 informed consent form 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 Case Report Form:

9.4.3.1. Relationship to the Study Drug

The event's relationship to the Study Drug (ISIS 766720 or placebo) is characterized by one of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug, 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 Study Drug administration

- **Unlikely:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug (ISIS 766720 or placebo) 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 Study Drug

9.4.3.2. Severity

The severity of AEs and SAEs relating to laboratory tests and adverse events 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 Study Drug (ISIS 766720 or placebo) due to the event is characterized by one of the following.

- **None:** No changes were made to Study Drug (ISIS 766720 or placebo) administration and dose
- **Permanently Discontinued:** Study Drug 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 and/or dosing frequency:** 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 one 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 one 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 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)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

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 Study Drug 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, the Sponsor or a designee should follow-up by telephone, fax, electronic mail, 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. 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 must 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

Study Drug (ISIS 766720 or placebo) 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 Case Report Form. If the patient takes a dose of Study Drug (ISIS 766720 or placebo) 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

Study Drug should be recorded on the Adverse Event eCRF. If the associated adverse event 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

Patients 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 Study Drug. 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 pregnancy progress and outcome**.** A longer follow-up may be required if the newborn child experiences a medical condition.

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. STATISTICAL CONSIDERATIONS

10.1. Study Endpoints, Subsets, and Covariates

10.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change in IGF-1 from Baseline to 28 Days after last dose (PTWk5 Visit).

10.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- Proportion of patients achieve normalized IGF-1 levels to within 1.2 times of gender and aged limits at 28 days after last dose (PTWk5 Visit)
- Proportion of patients achieve normalized IGF-1 levels to within 1.0 times of gender and aged limits at 28 days after last dose (PTWk5 Visit)
- Change from Baseline in serum IGF-1 over time
- Percent change from Baseline in serum IGF-1 over time

10.1.3. Tertiary and Pharmacodynamic Endpoints

The tertiary and pharmacodynamic endpoints include:

- Change from Baseline in growth hormone (GH) over time
- Percent change from Baseline in GH over time
- Change from Baseline over time in pharmacodynamic endpoints, including fasting plasma GHBP, acid-labile subunit (ALS), and insulin-like growth factor binding protein 3 (IGFBP3)
- Percent change from Baseline over time in pharmacodynamic endpoints, including fasting plasma GHBP, ALS, and IGFBP3

10.1.4. Exploratory Endpoints

The exploratory endpoints include:

- Glycemic parameters over time, including HbA1c, fasting plasma glucose and glycated albumin
- Glycemic parameters during 2-hour oral glucose tolerance test, including plasma glucose, insulin and C-peptide
- Acromegaly Quality of Life Questionnaire (AcroQoL)
- Acromegaly Symptom and Treatment Score Questionnaire (ASTS)
- Ring Size Assessment

10.1.5. Safety Endpoints

The safety endpoints include:

- Adverse events
- Vital signs and weight and calculated BMI
- Physical examination
- Clinical laboratory tests
- ECG
- Use of concomitant medication

10.2. Sample Size Considerations

Based on prior clinical trial experience, it is estimated that the standard deviation of the mean percent change from Baseline IGF-1 is approximately 20%. In the Per Protocol Set, with at least planned 10 patients in the pooled placebo group and 10 patients in an ISIS 766720 dose group, there will be at least 90% power to detect a 45% difference in mean percent change from Baseline IGF-1 between each of the ISIS 766720 dose groups and the pooled placebo group at an alpha level of 0.05.

10.3. Populations

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

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

Per Protocol Set (PPS): All FAS patients who complete at least 5 of the 6 doses of Study Drug with the first 3 doses administered on schedule 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 Study Drug and have at least one 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 Study Drug (ISIS 766720 or placebo).

10.5. Interim Analysis

To ensure patient safety, blinded data including the AEs and safety laboratory data will be reviewed by the Sponsor on an ongoing basis.

An interim analysis may be conducted when at least 6 patients in the higher strata (> 2.5 x ULN IGF-1) or at least 6 patients in the lower strata (≤ 2.5 × ULN IGF-1) complete the Week 11 (Study Day 71) assessments (2 weeks after Day 57 (e.g., 3 month) dose). Additional interim analysis for each cohort may also be conducted once each cohort completes the Post-Treatment Week 5 assessments. Unblinded data may be evaluated at this analysis for comparative safety

and efficacy. The Investigator, study staff, patients, monitors, Sponsor's Medical Monitor and members of the Sponsor's clinical operations team and data management team will remain blinded throughout the study. The analysis will be executed with controlled dissemination to ensure the integrity of ongoing data collection. Details of these controls will be described in the Statistical Analysis Plan (SAP).

10.6. Planned Methods of Analysis

The primary endpoint analysis will take place after all randomized patients complete Post-Treatment Week 5 and the database has been locked. The final analysis will take place after all randomized patients complete last visit of the Post-Treatment Period and the database has been locked.

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.

For data summaries and statistical analyses, the placebo patients from both cohorts will be pooled. The efficacy endpoints will be assessed on the FAS and Per Protocol Set 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 Study Drug (ISIS 766720 or placebo) received will be summarized by treatment group. The treatment-emergent adverse events (TEAEs) and SAEs will be summarized for each treatment group using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system, by system organ class, preferred term, relationship to Study Drug, 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, CBC with differential, coagulation panel, complement etc., will be summarized by study visits for each treatment group. These safety variables will also be presented as change and percent change from Baseline over time after Study Drug (ISIS 766720 or placebo) administration, as appropriate. Vital sign, calculated BMI, and ECG measures will be summarized by treatment group.

10.6.3. Efficacy Analysis

The primary analysis will be the comparison of percent change from Baseline to PTWk5 (28 days after last dose) in serum IGF-1 between an ISIS 766720 dose group and pooled placebo group in the Per Protocol Set. The data will be analyzed using analysis of variance (ANOVA)

with treatment and randomization stratification factor (screening IGF-1 level) as independent variables. In the case data departs substantially from normality, the nonparametric test, van Elteren Test, will be employed instead.

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

Additional secondary efficacy analyses are:

- Comparison of change and percent change from Baseline to each schedule post-baseline visit in serum IGF-1 between each of the ISIS 766720 dose groups and the pooled placebo group in the PPS and FAS. The data will be analyzed in a similar way to the primary analysis
- Difference between each of the ISIS 766720 dose groups and the pooled placebo group in the proportion of patients achieve normalized IGF-1 levels to within 1.2 times of gender and aged limits at PTWk5 (28 days after last dose) will be assessed by a Fisher's exact test in the PPS and FAS
- Difference between each of the ISIS 766720 dose groups and the pooled placebo group in the proportion of patients achieve normalized IGF-1 levels to within 1.0 times of gender and aged limits at PTWk5 (2 days after last dose) will be assessed by a Fisher's exact test in the PPS and FAS

Tertiary and pharmacodynamic analyses include:

- Comparison of change and percent change from Baseline to each scheduled post-baseline visit in GH between each of the ISIS 766720 dose groups and the pooled placebo group. The data will be analyzed in a similar way to the primary analysis in both the PPS and FAS
- Comparison of change and percent change from Baseline to each scheduled post-baseline visit in pharmacodynamic endpoints, including fasting plasma GHBP, acid-labile subunit (ALS), and IGFBP3, between each of the ISIS 766720 dose groups and the pooled placebo group. The data will be analyzed in a similar way to the primary analysis in both the PPS and FAS

10.6.4. Pharmacokinetic Analysis

Non-compartmental PK analysis of ISIS 766720 (as total full-length ASO) will be carried out on each individual patient data set. Calculated PK parameters may include: Maximum observed drug concentration (C_{max}), time to reach C_{max} (T_{max}), area under the concentration-time curve from time zero (pre-dose) to select times after dose administration (AUC_t), and the plasma half-life ($t_{1/2\lambda z}$) associated with the terminal disposition phase. Additional PK parameters may be calculated at the discretion of the PK analyst. Population PK analysis and PK/PD analysis with relevant PD biomarker levels using data from this study or in combination with data from other ISIS 766720 studies may be performed if deemed appropriate.

10.6.5. Additional Analyses

The exploratory analyses include:

- Comparison of change and percent change from Baseline to each scheduled post-baseline visit in Glycemic parameters, including HbA1c, and fasting plasma glucose and glycate albumin between each of the ISIS 766720 dose groups and the pooled placebo group. The data will be analyzed in a similar way to the primary analysis in both the Per Protocol Set and FAS.
- Comparison of change and percent change from Baseline to each scheduled post-baseline visit in Glycemic parameters during 2 hours oral glucose tolerance test, including plasma glucose, insulin and C-peptide, between each of the ISIS 766720 dose groups and the pooled placebo group. The data will be analyzed in a similar way to the primary analysis in both the Per Protocol Set and FAS.
- Comparison of change and percent change from Baseline to each scheduled post-baseline visit in AcroQoL, ASTS and Ring Size between each of the ISIS 766720 dose groups and the pooled placebo group. The data will be analyzed in a similar way to the primary analysis in both the Per Protocol Set and FAS.

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 any Study Drug (ISIS 766720 or placebo) 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 informed consent form 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 informed consent form 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 (IEC)/Institutional Review Board (IRB)

A copy of the protocol proposed informed consent form, 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 informed consent form must be received by the Sponsor before recruitment of patients into the study and shipment of Study Drug. 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 th

e Sponsor before recruitment of patients into the study and shipment of Study Drug. 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 informed consent forms) 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, Study Drug Product Accountability Record, Return of Study Drug Product for Destruction, final Study Drug 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

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14. APPENDICES

APPENDIX A. SCHEDULE OF PROCEDURES

Appendix A Schedule of Procedures

Study Period	**Screen**	**Treatment Period**								
Study Week	**-9 to -1**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**16**
Study Day	**-63 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**112[A]**
Visit Window ± Day	**0**	**0**	**3**	**5**	**5**	**5**	**5**	**5**	**5**	**3**
Home Health Care Visit Option[B]					**X**		**X**		**X**	
Informed Consent	X									
Inclusion/Exclusion	X									
Medical History	X									
Disease History	X									
MRI of sellar (if no prior MRI results within the last 6 months) or CT when MRI contraindicated	X									
AcroQoL		X[a]				X[a]				X[a]
ASTS[17]		X[a]		X[a]		X[a]		X[a]		X[a]
Ring Size Measurement[18]	X	X[a]		X[a]		X[a]		X[a]		X[a]
Body Weight and Height[1]	X	X		X		X		X		
Vital Signs[2]	X	X[a]	X[a]	X[a]	X	X[a]	X	X[a]	X	X[a]
Physical Exam[3]	X	X		X		X		X		X
ECG (12-Lead) in Triplicate[4]	X	X[a]		X		X		X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
HIV, Hepatitis B & C	X									
FSH[6]	X									
Pregnancy Test[7]	X	X[a]		X[a]		X[a]		X[a]		X[a]
Chemistry Panel (Fasting)[8, 9]	X	X[a]	X[a]	X[a]	X	X[a]	X	X[a]	X	X[a]
Hematology[9]	X	X[a]	X[a]	X[a]	X	X[a]	X	X[a]	X	X[a]
Partial PD Panel: GH, IGF-1, GHBP[8]			X[a]		X		X		X	

Appendix A Schedule of Procedures *Continued*

Study Period	**Screen**	**Treatment Period**								
Study Week	**-9 to -1**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**16**
Study Day	**-63 to -1**	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**112[A]**
Visit Window ± Day	**0**	**0**	**3**	**5**	**5**	**5**	**5**	**5**	**5**	**3**
Home Health Care Visit Option[B]					**X**		**X**		**X**	
Full PD Panel[8,]	X	X[a]		X[a]		X[a]		X[a]		X[a]
hs CRP		X[a]	X[a*]	X[a*]						
PT, INR, aPTT	X	X[a]		X[a]		X[a]		X[a]		
Pituitary Axis[19], Thyroid panel	X					X[a]				
Bone Biomarker		X[a]				X[a]				
Lipid panel[8]	X	X[a]				X[a]				
Screening HbA1c	X									
Glycemic Panel (Including HbA1c) and 2-hr. OGTT[8, a]		X[16, a,b]				X[a,b]				
Archived Serum Sample[11]	X	X[a]				X[a]				
Immunogenicity Testing		X[a]		X[a]		X[a]		X[a]		X[a]
PK Blood Sampling[12]		X[d]	X[a]	X[a]		X[a]		X[a]		X[d]
Urinalysis[13]	X	X[a]	X[a]	X[a]	X	X[a]	X	X[a]	X	X[a]
Study Drug (ISIS 766720 or placebo) Administration		X	X	X		X		X		X
Somatostatin Receptor Ligand (SRL)[10]		X[c]		X[c]		X[c]		X[c]		X[c]
Patient Contact Option	If a visit cannot be performed, patient contact is required by site personnel to assess Adverse Events and Concomitant Medications									

Appendix A Schedule of Procedures *Continued*

Study Period	**Post-Treatment Period (14 Weeks)**						
Study Week (Wk) from Last Dose	**PTWk3**	**PTWk5**	**PTWk7**	**PTWk11**	**PTWk15**	**ETTX[14,15]**	**ETPT[14,15]**
Study Day from Last Dose	**PTD15[15]**	**PTD29[15]**	**PTD43[15]**	**PTD71[15]**	**PTD99[15]**	**NA**	**NA**
Study Day from Day 1	**127**	**141**	**155**	**183**	**211**	**NA**	**NA**
Visit Window ±	**5**	**3**	**5**	**5**	**5**	**NA**	**NA**
Home Health Care Visit Option[B]	**X**		**X**				
MRI of Sellar or CT when MRI contraindicated	MRI/CT after treatment if clinically indicated as assessed by Sponsor and Investigator						
AcroQoL		X		X	X	X	X
ASTS[17]	X	X	X	X	X	X	X
Ring Size Measurement[18]	X	X	X	X	X	X	X
Body Weight		X			X	X	X
Vital Signs[2]	X	X	X	X	X	X	X
Physical Exam[3]		X		X	X	X	X
ECG (12-Lead) in Triplicate[4]		X		X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Pregnancy Test[7]		X		X	X	X	X
Chemistry Panel (Fasting)[8, 9]	X	X	X	X	X	X	X
Hematology[9]	X	X	X	X	X	X	X
Partial PD Panel: GH, IGF-1, GHBP[8]			X				
Full PD Panel[8]	X	X		X	X	X	X
hs CRP		X*				X*	
PT, INR, aPTT		X			X	X	X
Pituitary Axis[19], Thyroid panel		X			X	X	X
Bone Biomarker		X			X	X	X

Appendix A Schedule of Procedures *Continued*

Study Period	**Post-Treatment Period (14 Weeks)**						
Study Week (Wk) from Last Dose	**PTWk3**	**PTWk5**	**PTWk7**	**PTWk11**	**PTWk15**	**ETTX[14,15]**	**ETPT[14,15]**
Study Day from Last Dose	**PTD15[15]**	**PTD29[15]**	**PTD43[15]**	**PTD71[15]**	**PTD99[15]**	**NA**	**NA**
Study Day from Day 1	**127**	**141**	**155**	**183**	**211**	**NA**	**NA**
Visit Window ±	**5**	**3**	**5**	**5**	**5**	**NA**	**NA**
Home Health Care Visit Option[B]	**X**		**X**				
Lipid panel[8]		X			X	X	X
Glycemic Panel and 2 hr OGTT[8,a]		X[b]				X[b]	
Archived Serum Sample[11]		X			X	X	X
Immunogenicity Testing	X	X	X	X	X	X	X
PK Blood Sampling[12]	X	X	X	X	X	X	X
Urinalysis[13]	X	X	X	X	X	X	X
Somatostatin Receptor Ligand (SRL)[10]	Patient will remain on stable SRL monthly dosing regimen						
Patient Contact Option	If a visit cannot be performed, patient contact is required by site personnel to assess Adverse Events and Concomitant Medications						

A Please note this visit is at the end of the 16th week at Day 112

B 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. These assessments should be attempted at the next clinic visit if not performed at the Home Health Care visit. A confirmation of ISIS 766720 dosing by the Home Health Provider should be obtained and documented in source within 48 hours.

1 Height at screening only

2 BP, HR, RR, temperature

3 Full physical exam to be given at screening and abbreviated physical exam to be given during treatment and Follow-up Period as indicated to assess changes from screening

4 Triplicate ECG study procedure will consist of 3 ECGs with 2 minutes between each ECG (± 2 mins window between each assessment)

5 (Left intentionally blank)

6 FSH: 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

Appendix A Schedule of Procedures *Continued*

[7] A pregnancy test is required for women who are of childbearing potential regardless of age. Serum at Screening, Dipstick acceptable after Screening. For patients requiring confirmation of menopause at Screening per protocol, a pregnancy test is required at Screening, however, once menopausal status is confirmed, a pregnancy test is not required in subsequent visits

[8] Fasting is not required at Screening Visit. Fasted samples should be taken after fasting for 8 hours (or 10 hours prior to OGTT). During this time the patient can drink water and they should ensure that they consume sufficient water in order 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 over a period greater than 21 days (per Section 8.5.2), the test must be repeated or drawn and a result not meeting stopping rule must be obtained prior to next dose. In consultation with the Medical Monitor a local lab and central lab may be drawn and evaluated prior to dosing (per Section 6.2.1).

[10] Plan to align all SRL injections to be either i) the same day as the Study Drug administration, or ii) up to 3 days after the Study Drug administration. If dosing is not done in the clinic, the date and time of each SRL dose will be documented by the patient in a SRL dosing diary and provided to the study center staff at subsequent visits. The window for SRL dosing is 1-3 days after Study Drug administration. The visit window in the Schedule of Procedures table is not applicable to SRL dosing

[11] 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.)

[12] If time is not specified PK draw can be done at anytime

[13] If hematuria or 2+ proteinuria is observed, see confirmation guidance in Section 8.5

[14] If patient terminates early from the Treatment Period, an early termination visit from treatment (ETTX) is required as soon as possible. After ETTX visit, patient should continue in Post-Treatment Period, following the schedule in intervals relative to patient's last dose. Patient terminating from the Post-Treatment Period should complete the early termination visit from post-treatment (ETPT)

[15] PT = Post-Treatment visit; ETTX = Early Termination visit from treatment; ETPT = Early Termination visit from Post-Treatment Period

[16] The Day 1 OGTT can be conducted between Day -7 and Day-1. The procedure can be conducted in the clinic or as arranged by a Home Health Care professional. After the 120-min blood draw, the fasting period is completed

[17] Patients should leave ASTS Question #5 blank for Day 1 and Post-Treatment Days 127, 141, 155, 183, 211, and ETPT

[18] If possible, the same study personnel should conduct the ring size assessment at each clinic visit

[19] A morning cortisol sample is required, and the sample should be drawn prior to 09:00

Time (time is in hours relative to Study Drug administration):

[a] Pre-dose

[b] -5, 0, 30, 60, 90, 120 mins (Note: The 2-hr. OGTT is conducted prior to Study Drug administration during the Treatment Period, these times are relative to oral glucose ingestion)

[c] Any time after ISIS 766720 or placebo injection

[d] Pre-dose, 1, 2, 4, 6 hours

* May be analyzed

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

Screening Tests
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (women only)
- Serum βhCG

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

PD Panel (*Partial Panel)
- IGF-1*
- GH*
- GHBP*
- ALS
- IGFBP3

Glycemic Panel
- HbA1c
- Glucose
- glycated albumin
- During OGTT: Glucose, insulin and C-peptide

Pituitary Axis
- Morning Cortisol (before 09:00)
- ACTH
- Prolactin

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

Thyroid Panel
- TSH
- Free T4
- Total T3

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

Pharmacokinetics[1]
- ISIS 766720 levels in plasma

Immunogenicity[1]
- Anti-ISIS 766720 antibodies

Inflammatory
- hs-CRP

Urinalysis
- Color
- Appearance
- Specific gravity
- pH
- P/C Ratio
- A/C Ratio
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- Microscopic examination[2]

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

[1] 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

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

APPENDIX C. PK SAMPLING SCHEDULE

Appendix C PK Sampling Schedule

Treatment Period						Post-Treatment Period					Early Terminate from Treatment	Early Terminate from Post-Treatment
Week 1	**Week 3**	**Week 5**	**Week 9**	**Week 13**	**Week 16**	**PTWk3**	**PTWk5**	**PTWk7**	**PTWk11**	**PTWk15**		
D1	**D15**	**D29**	**D57**	**D85**	**D112**	**D127**	**D141**	**D155**	**D183**	**D211**	**ETTX**	**ETPT**
Blood: Pre-dose, 1, 2, 4, 6 hours Post-SC Injection	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose, 1, 2, 4, 6 hours Post-SC Injection	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime	Blood: Anytime

Note: If 6-hour PK sampling is not possible a protocol deviation can be entered

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 adverse events relating to lab test abnormalities are based upon the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017.

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:	2
Version Date:	20 May 2020
Title:	ISIS 766720-CS2 Amend 4 - A DB, Placebo-Controlled, Phase 2 Study to Assess Safety, Tolerability, & Efficacy of 766720 Administered Once Every 28D for 16 Wks in Pts w/Acromegaly Being Treated w/Long-acting SRL

APPROVALS:

[redacted]
[redacted] 20-May-2020 16:47:05 GMT+0000

Official Title:	**A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of ISIS 766720 (IONIS-GHR-LRx, an Antisense Inhibitor of the Growth Hormone Receptor) Administered Once Every 28 Days for 16 Weeks in Patients With Acromegaly Being Treated With Long-acting Somatostatin Receptor Ligands (SRL)**
NCT Number:	NCT03548415
Document Dates:	Statistical Analysis Plan Version 2.0: 05-March-2021

1.9 Documentation of Statistical Methods

Statistical Analysis Plan, Version 2.0 (5 March 2021), is provided.

Name:	766720-CS02 Statistical Analysis Plan 05 Mar 2021
Version:	2

APPROVALS:

[redacted] Approved 05-Mar-2021 20:22:56 GMT+0000 [redacted] Approved 05-Mar-2021 20:32:06 GMT+0000 [redacted] Approved 05-Mar-2021 22:17:34 GMT+0000 [redacted] Approved 08-Mar-2021 16:28:54 GMT+0000

Statistical Analysis Plan

ISIS 766720 –CS2

A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of ISIS 766720 (IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor) Administered Once Every 28 Days for 16 Weeks in Patients with Acromegaly Being Treated with Long-acting Somatostatin Receptor Ligands (SRL)

Date: March 5, 2021

Version: 2.0

CONFIDENTIAL

Ionis Pharmaceuticals, Inc.

2855 Gazelle Court Carlsbad, CA 92010

Compound Name: 766720

Protocol: CS2

Study Title: A Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Safety, Tolerability, and Efficacy of ISIS 766720 (IONIS GHR-L_{RX}, an Antisense Inhibitor of the Growth Hormone Receptor) Administered Once Every 28 Days for 16 Weeks in Patients with
Acromegaly Being Treated with Long-acting Somatostatin Receptor Ligands (SRL)

Issue Date: 18 MAY 2020 (Protocol Amendment 4)

See electronic signature and date attached to this document

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Table of Contents

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 randomized, double blind, placebo-controlled, Phase 2 study to assess the safety, tolerability, and efficacy of ISIS 766720 administered once every 4 weeks for 16 weeks to patients with acromegaly uncontrolled (IGF-1 level between 1.3 x to 5 x ULN) on select long-acting SRL. Patients will be stratified by the screening IGF-1 level (IGF-1 > 2.5 x ULN or ≤ 2.5 x ULN age and sex adjusted by central lab).

This study will be conducted at multiple centers worldwide at approximately 40 sites. Approximately 60 patients are planned to be randomized in their corresponding randomization ratio (ISIS 766720 vs. Placebo) are as following:

Cohort A: ISIS 766720 60 mg + SRL or placebo + SRL (2 active :1 placebo) every 28 days. In addition, a booster dose of Study Drug is administered on Day 15. Total of 15 patients are enrolled.

Cohort B: ISIS 766720 80 mg + SRL or placebo + SRL (2 active :1 placebo) every 28 days. In addition, a booster dose of Study Drug is administered on Day 15. Total of 15 patients are enrolled.

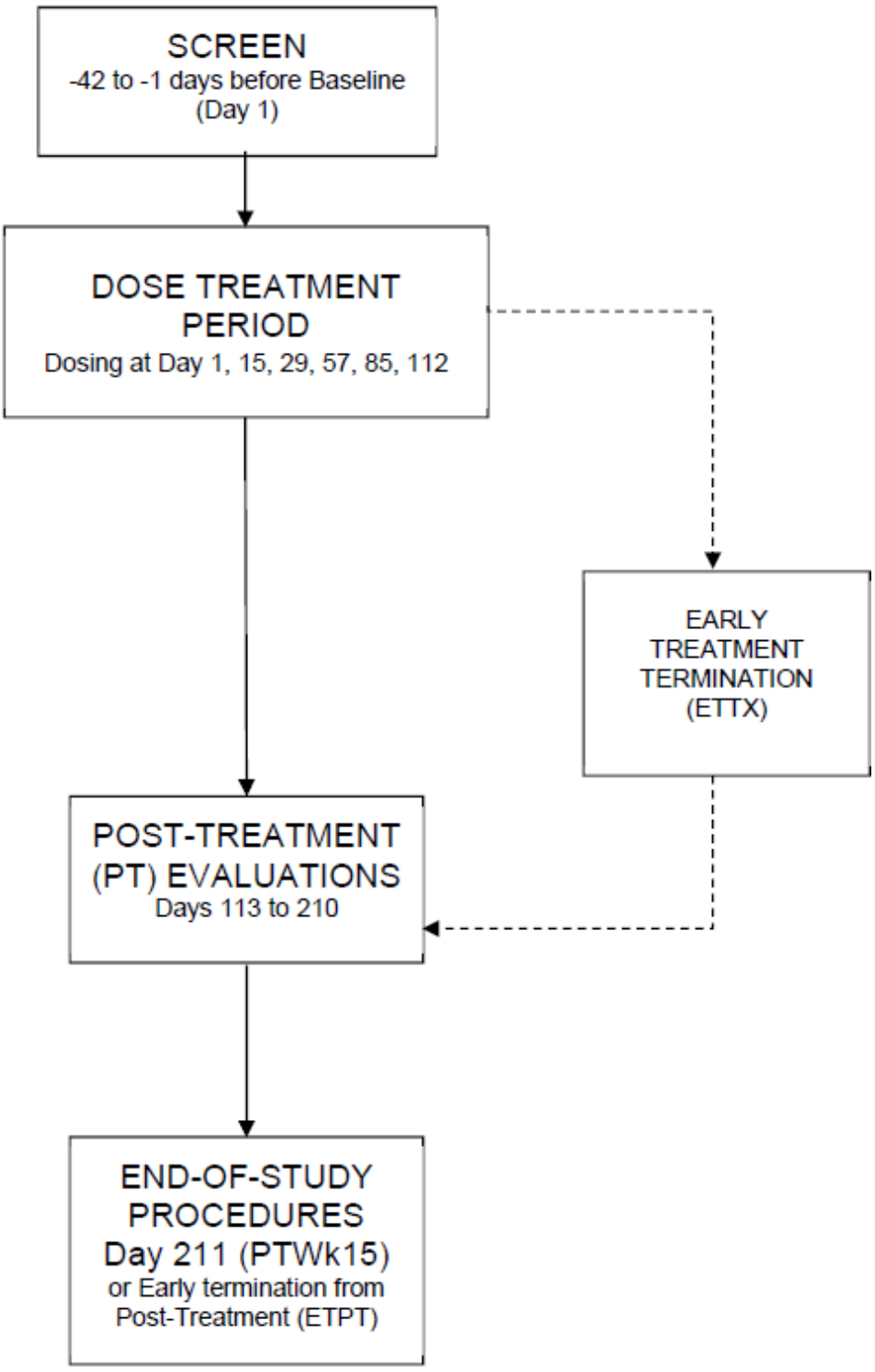
Cohort C: ISIS 766720 120 mg + SRL or placebo + SRL (5 active :1 placebo) every 28 days. In addition, a booster dose of Study Drug is administered on Day 15. Total of 12 patients are enrolled.

Cohort D: ISIS 766720 160 mg + SRL or placebo + SRL (5 active :1 placebo) every 28 days. In addition, a booster dose of Study Drug is administered on Day 15. Total of 12 patients are enrolled.

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

- A ≤ 6-week Screening Assessment Period
- A 16-week Treatment Period during which Study Drug will be administered as a once every 28 days SC injection (except during Month 1 where a booster dose is administered on Day 15)
- A 14-week Post-Treatment Evaluation Period

The study design and treatment schema are depicted as follows:


SCREEN
-42 to -1 days before Baseline
(Day 1)
DOSE TREATMENT PERIOD
Dosing at Day 1, 15, 29, 57, 85, 112
EARLY TREATMENT TERMINATION (ETTX)
POST-TREATMENT (PT) EVALUATIONS
Days 113 to 210
END-OF-STUDY PROCEDURES
Day 211 (PTWk15)
or Early termination from Post-Treatment (ETPT)

1.2 Objective

1.2.1 Primary Objectives

To evaluate the efficacy of ISIS 766720 subcutaneous (SC) injection on serum insulin-like growth factor 1 (serum IGF-1) vs. placebo as an add-on therapy to long acting somatostatin receptor ligands (SRL) octreotide and lanreotide.

To evaluate the safety and tolerability of ISIS 766720 SC injection vs. placebo as add-on therapy to SRL.

1.2.2 Secondary Objective

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

1.2.3 Tertiary Objectives

To evaluate the effects of ISIS 766720 SC injection on GH over time.

To evaluate the effects of ISIS 766720 SC injection on the following pharmacodynamic endpoints: fasting plasma GHBP, ALS, IGFBP3.

1.2.4 Exploratory Objectives

To evaluate the effects of ISIS 766720 SC injection on the following glycemic parameters: HbA1c, fasting plasma glucose, glycated albumin as well as glucose, insulin and C-peptide during 2-hour oral glucose tolerance test.

To evaluate the effects of ISIS 766720 SC injection on the clinical endpoints using AcroQoL, acromegaly sign and symptom treatment score questionnaire (ASTS) and ring size measurement.

To evaluate pharmacokinetic (PK) exposure over time and potential PK/PD correlation on relevant biomarkers.

1.3 Endpoints

1.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change in IGF-1 from Baseline to 28 Days after last dose (PTWk5 Visit).

1.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- Proportion of patients achieve normalized IGF-1 levels to within 1.2 times of gender and aged limits at 28 days after last dose (PTWk5 Visit)
- Proportion of patients achieve normalized IGF-1 levels to within 1.0 times of gender and aged limits at 28 days after last dose (PTWk5 Visit)
- Change from Baseline in serum IGF-1 over time
- Percent change from Baseline in serum IGF-1 over time

1.3.3 Tertiary and Pharmacodynamic Endpoints

The tertiary and pharmacodynamic endpoints include:

- Change from Baseline in growth hormone (GH) over time
- Percent change from Baseline in GH over time
- Change from Baseline over time in pharmacodynamic endpoints, including fasting plasma GHBP, acid-labile subunit (ALS), and insulin-like growth factor binding protein 3 (IGFBP3)
- Percent change from Baseline over time in pharmacodynamic endpoints, including fasting plasma GHBP, ALS, and IGFBP3

1.3.4 Exploratory Endpoints

The exploratory endpoints include:

- Glycemic parameters over time, including HbA1c, fasting plasma glucose and glycated albumin
- Glycemic parameters during 2-hour oral glucose tolerance test (OGTT), including plasma glucose, insulin and C-peptide
- Acromegaly Quality of Life Questionnaire (AcroQoL)
- Acromegaly Symptom and Treatment Score Questionnaire (ASTS)
- Ring Size Assessment

1.3.5 Safety Endpoints

The safety endpoints include:

- Adverse events
- Vital signs and weight and calculated Body mass index (BMI)
- Physical examination
- Clinical laboratory tests
- Electrocardiogram (ECG)
- Use of concomitant medication

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 LMU Munich via Medpace Reference Laboratories, and from PPD Development (plasma concentration data) to Ionis Pharmaceuticals, Inc.

2.2 Randomization

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

Eligible patients will be stratified based on screening IGF-1 levels (≤ 2.5 x ULN or > 2.5 x ULN age and sex adjusted by central lab) and then patients will be randomized to 1 of 2 dose cohorts in a 1:1 ratio (Cohort A or Cohort B). Within each dose cohort, patients will be further randomized to receive ISIS 766720 or placebo in a 2:1 ratio.

Eligible patients for Cohorts C and D will be stratified based on screening IGF-1 levels (≤ 2.5 x ULN or > 2.5 x ULN, age and sex adjusted by central lab). Patients will be randomized to receive ISIS 766720 or placebo in a 5:1 ratio.

After enrollment in Cohort A and B is completed, Cohort C will begin enrollment. Cohort D may be conducted based on the safety and efficacy results of the lower-dose cohorts.

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), are 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 study site.

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 (CRF) Data

BioClinica (or designee) is responsible for creating the Electronic Data Capture (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 are corrected or an explanation concerning the query is provided in the EDC system. After all data are entered, reviewed (by Data Management and Clinical Development) and queried, and all queries resolved, the database is locked.

2.5.2 Laboratory Data

Ionis Pharmaceuticals, Inc. is responsible for the format of the laboratory electronic data transfers, transfer schedule and review of the clinical laboratory data. This lab data will be stored as SAS data sets or Excel files.

2.5.3 Pharmacokinetics (PK) Data

Ionis Pharmaceuticals, Inc. is responsible for the management and review of the plasma drug concentration data. This process involves reviewing the patient and visit identifiers (i.e., patient demographics) with the clinical data collected in the EDC system. The PK data are not stored in the EDC system.

3 ANALYSIS PLAN

3.1 General Overview of Analyses

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 used to summarize most data. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated.

PK parameters will be summarized to include number of patients, mean, standard deviation, coefficient of variation (CV), geometric mean, median, minimum, and maximum.

Pooled groups:

Patients who are placebo-treated will be pooled and analyzed as a single placebo group. Patients who are ISIS 766720-treated may be pooled and summarized as the ISIS 766720 low dose, and ISIS 766720 high dose, or total ISIS 766720 treated group.

Baseline definition:

Unless otherwise specified, baseline is defined as the last non-missing value prior to the first administration of Study Drug (ISIS 766720 or placebo).

The baseline for Platelets is defined as the average of all values prior to the first administration of Study Drug (ISIS 766720 or placebo).

Analytical visits:

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, but will be presented in data listings.

3.2 Sample Size Considerations

Based on prior clinical trial experience, it is estimated that the standard deviation of the mean percent change from Baseline IGF-1 is approximately 20%. In the per protocol set, with 10 patients in the pooled placebo group and 10 patients in each ISIS 766720 dose group, there will be at least 90% power to detect a 45% difference in mean percent change from Baseline IGF-1 between each of the ISIS 766720 dose groups and the pooled placebo group at an alpha level of 0.05.

3.3 Scoring of Questionnaires and Ring Size Assessment

3.3.1 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:

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

Here Y is the re-calculated score, and X is the sum of all the item responses within the dimension or study 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).

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

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.

3.3.2 Acromegaly Symptom and Treatment Score Questionnaire (ASTS)

ASTS is an Ionis internally developed questionnaire to assess acromegaly symptom and treatment, which contains 6 items (Table 2).

Table 2: The ASTS Questionnaire

Item	Question	Response				
1	I HAVE HEADACHES THAT LAST ALL DAY OR OVER MULTIPLE DAYS DESPITE MEDICATION	Always	Most of the time	Sometimes	Rarely	Never
2	I EXPERIENCE EXCESSIVE SWEATING	Always	Most of the time	Sometimes	Rarely	Never
3	I FEEL PUFFY, OR HAVE SWOLLEN FEET OR LEGS	Always	Most of the time	Sometimes	Rarely	Never
4	I EXPERIENCE LOSS OF SENSATION OR NUMBNESS OR TINGLING IN MY HANDS	Always	Most of the time	Sometimes	Rarely	Never
5	THE STUDY DRUG INJECTION IS BOTHERSOME TO ME	Completely Agree	Moderately Agree	Neither Agree nor Disagree	Moderately Disagree	Completely Disagree
6	I EXPERIENCED INCREASED HEADACHE, SWELLING, OR EXCESS SWEATING IN THE LAST FEW DAYS BEFORE THIS UPCOMING LANREOTIDE / OCTREOTIDE INJECTION	Completely Agree	Moderately Agree	Neither Agree nor Disagree	Moderately Disagree	Completely Disagree

Each of the 6 items of the ASTS 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 the acromegaly symptom and treatment.

The item 5 question does not apply to study Day 1 and post-treatment assessments, since the ASTS questionnaire is completed prior to receiving study drug injection on Day 1, and no study drug is administered during the post-treatment period. No change and percent change from baseline analyses will be performed for item 5, since no baseline (Day 1) is available for item 5.

Each of the 6 items will be analyzed individually. If the response to an item is missing at a visit, it will not be included in the analysis for that item at that visit. The range of the individual score for each item is 1 to 5.

In addition, a composite score (Acromegaly Symptom Composite Score) will be calculated by summing the ASTS item 1, item 2, item 3, and item 4 scores. If 1 or more of the 4 items has missing response, the Acromegaly Symptom Composite Score will not be calculated. The range of this composite score is 4 to 20.

3.3.3 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.

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.

3.4 Statistical Methods

3.4.1 Patient Population Analyzed

The following analysis populations are defined for this study:

- Safety Set: All patients who are randomized and receive at least 1 dose of Study Drug.
- Full Analysis Set (FAS): All randomized patients who receive at least 1 dose of ISIS 766720 or placebo and have at least 1 post-baseline efficacy or pharmacodynamic assessment.
- Per Protocol Set (PPS): All FAS patients who complete at least 5 of the 6 doses of Study Drug with the first 3 doses administered on schedule 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 one evaluable PK sample.

3.4.2 Handling of Missing Data

Unless otherwise specified, missing values will not be imputed.

3.4.3 Planned Interim Analysis

To ensure patient safety, blinded data including the AEs and safety laboratory data will be reviewed by the Sponsor on an ongoing basis.

An interim analysis may be conducted when at least 6 patients in the higher strata (> 2.5 x ULN IGF-1) or at least 6 patients in the lower strata (≤ 2.5 x ULN IGF-1) complete the Week 11 (Study Day 71) assessments (2 weeks after Day 57 (e.g., 3 month) dose). Unblinded data may be evaluated at this analysis for comparative safety and efficacy. The Investigator, study staff, patients, monitors, Sponsor's Medical Monitor and members of the Sponsor's clinical operations team and data management team will remain blinded throughout the study. The analysis will be executed with controlled dissemination to ensure the integrity of ongoing data collection. The individuals involved in the unblinded interim analysis will be identified and documented at the time of unblinded interim analysis according to Ionis standard operation procedure (SOP).

3.5 Demographic and Baseline Characteristics

Demographic and Baseline characteristics (e.g., age, gender, ethnicity, race, weight, height, BMI) will be summarized using descriptive statistics by treatment group.

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

Patient randomization and disposition will be summarized by cohort and treatment group. All patients enrolled will be included in the summary of disposition.

Protocol deviations will be listed.

3.6 Efficacy (Pharmacodynamic) Analysis

3.6.1 Primary Efficacy Analysis

The primary analysis will be the comparison of percent change from Baseline to PTWk5 (28 days after last dose) in serum IGF-1 between an ISIS 766720 dose group and pooled placebo group in the Per Protocol Set. The data will be analyzed using analysis of variance (ANOVA) with treatment and randomization stratification factor (screening IGF-1 level) as independent variables. The normality assumption for the ANOVA model will be assessed by the Shapiro-Wilks test on the residuals. In the case data departs substantially from normality, the nonparametric test, van Elteren Test, will be employed instead. Additional analysis with baseline IGF-1 actual level as a covariate may be conducted.

The primary analysis will take place after all patients complete Treatment Period and the database has been locked.

3.6.2 Secondary Efficacy Analysis

3.6.2.1 Secondary analysis on the primary efficacy endpoint

Comparison of percent change from Baseline to PTWk5 (28 days after last dose) in serum IGF-1 between an ISIS 766720 dose group and pooled placebo group in the FAS will be carried out. The data will be analyzed in a similar way to the primary analysis.

3.6.2.2 Additional secondary efficacy analyses

- Comparison of change and percent change from Baseline to each schedule post-baseline visit in serum IGF-1 between each of the ISIS 766720 dose groups and the pooled placebo group in the PPS and FAS. The data will be analyzed in a similar way to the primary analysis
- Difference between each of the ISIS 766720 dose groups and the pooled placebo group in the proportion of patients achieve normalized IGF-1 levels to within 1.2 times of gender and aged limits at PTWk5 (28 days after last dose) will be assessed by Fisher's exact test in the PPS and FAS
- Difference between each of the ISIS 766720 dose groups and the pooled placebo group in the proportion of patients achieve normalized IGF-1 levels to within 1.0 times of gender and aged limits at PTWk5 (28 days after last dose) will be assessed by Fisher's exact test in the PPS and FAS

For the proportion difference, additional analyses may be conducted by logistic regression to consider additional covariates.

3.6.3 Tertiary and Pharmacodynamic Analyses

The following analyses will be performed:

- Comparison of change and percent change from Baseline to each scheduled post-baseline visit in GH between each of the ISIS 766720 dose groups and the pooled placebo group. The data will be analyzed in a similar way to the primary analysis in both the PPS and FAS
- Comparison of change and percent change from Baseline to each scheduled post-baseline visit in pharmacodynamic endpoints, including fasting plasma GHBP, acid-labile subunit (ALS), and IGFBP3, between each of the ISIS 766720 dose groups and the pooled placebo group. The data will be analyzed in a similar way to the primary analysis in both the PPS and FAS

Additional analyses may be conducted to explore the relationship among PDs.

3.6.4 Exploratory Analyses

The exploratory analyses include:

- Comparison of change and percent change from Baseline to each scheduled post-baseline visit in Glycemic parameters, including HbA1c, and fasting plasma glucose and glycate albumin between each of the ISIS 766720 dose groups and the pooled placebo group. The data will be analyzed in a similar way to the primary analysis in both the Per Protocol Set and FAS.

- Comparison of change and percent change from Baseline to each scheduled post-baseline visit in Glycemic parameters during 2 hours OGTT, including the area under curve (AUC) and the incremental AUC of plasma glucose, insulin and C-peptide, between each of the ISIS 766720 dose groups and the pooled placebo group. The data will be analyzed in a similar way to the primary analysis in both the Per Protocol Set and FAS.
- Comparison of change and percent change from Baseline to each scheduled post-baseline visit in AcroQoL (Global AcroQoL, Physical Dimension, Psychological Dimension, Appearance Sub-dimension, Personal Relationships Sub-dimension), ASTS and Ring Size between each of the ISIS 766720 dose groups and the pooled placebo group. The data will be analyzed in a similar way to the primary analysis in both the Per Protocol Set and FAS.

Change and percent change from Baseline to each scheduled post-baseline visit in glycemic parameters during 2 hours OGTT, including the area under curve (AUC) and the incremental AUC (iAUC) of plasma glucose, insulin and C-peptide, will be summarized. The AUC will be calculated for plasma glucose, insulin and C-peptide taken between 0 to 120 minutes responses to the OGTT. The plasma measurement taken prior to start time of glucose ingestion (defined as T0 time) will be used as the T0 plasma glucose and all subsequent time point will be relative to this T0 in the AUC calculation. The actual sample time (defined by the sample time relative to the defined T0 time) will be used in the AUC calculation. If a scheduled 120 minutes result is missing, then the AUC will not be calculated. If the actual sample time of the scheduled 120 mins result is more than 135 mins or less than 105 mins, then the AUC will also not be calculated. If a scheduled result at other timepoints is missing, the data will be linearly interpolated using the results prior to and immediate after the missing result.

The iAUC is defined as total AUC minus the rectangle area under basal (i.e., T0 plasma glucose measurement multiplied by actual sample time).

Additional analyses for the AcroQoL and ASTS may be described in the other analysis plan for exploratory purpose.

3.6.5 Subgroup analysis on the glycemic parameters

The comparison of change and percent change from Baseline to PTWk5 (28 days after last dose) in HbA1c and Glycemic parameters during 2 hours OGTT, including AUC and incremental AUC of plasma glucose and C-peptide, between each of the ISIS 766720 dose groups and pooled placebo group will be performed on the following baseline HbA1c subgroups in the PPS:

- <5.7% vs. >=5.7%
- <6.5% vs. >=6.5%
- <7.5% vs. >=7.5%
- <8.0% vs. >=8.0%
- <8.5% vs. >=8.5%
- <9.0% vs. >=9.0%
- <6.5% vs. 6.5-8% vs. >8%

The data will be analyzed in a similar way to the primary analysis.

3.7 Pharmacokinetic Analysis

Pharmacokinetic (PK) analysis will be conducted in the PK Population. The plasma PK of ISIS 766720 (as total full-length oligonucleotide or ISIS 766720-equivalent [ISIS 766720-eq.]) will be assessed following first and last SC dose administration(s).

Metabolite identification and profiling may be determined in some of the collected plasma samples and will be reported separately.

3.7.1 Plasma Concentration Data of Total Full-Length Oligonucleotides

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) will be listed (when applicable) for each patient, by treatment group, dose cohort, nominal dose, 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 indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %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 and %CV, as well as geometric mean and geometric% CV, will be reported as not applicable. Summary statistics of the ISIS 766720-eq plasma concentrations will be tabulated by treatment group, dose cohort, nominal dose, day, and scheduled time point. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

ISIS 766720-eq. plasma trough (pre-dose) and post-treatment concentration versus time (actual) profiles for each individual patient that received ISIS 766720 active treatment, as well as the mean (± SD or SE) plasma concentrations versus time (scheduled) profiles following first and last dose, will be presented graphically on linear and semilogarithmic scales without and with stratification by patient immunogenicity status (see Section 3.7.4). At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times.

3.7.2 Plasma Pharmacokinetic Parameters

The plasma PK of ISIS 766720 (as total full-length ASO) will be assessed following first- and last-dose SC administration(s). Non-compartmental pharmacokinetic analysis of ISIS 766720 (as total full-length ASO) will be carried out on each individual patient data set where full PK sampling profiles and/or 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 Day 1 and Day 112.

2. T_{max}: the time at which C_{max} occurs will be determined on Day 1 and Day 112.
3. $AUC_{0\text{-}6hr}$: partial area under the plasma concentration-time curve (AUC) from time zero to 6 hours will be calculated using the linear-up log-down trapezoidal rule on Day 1 and Day 112.
4. $CL_{0\text{-}6hr}$ /F (L/hr): partial clearance (e.g. 6 hr) divided by F (fraction of the dose absorbed) determined by Dose/$AUC_{0\text{-}6hr}$will be determined on Day 1 and Day 112.
5. $t_{1/2\lambda z}$: 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 coefficient of determination values (r^2 adjusted) has to be at or greater than 0.8 for the estimate to be accepted. This parameter will only be calculated following the dose on Day 112 for all evaluable patients receiving active study drug.

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

3.7.3 Pharmacokinetic/Pharmacodynamic Exposure-Response Analysis

Exposure-response correlations may be explored graphically between plasma exposure (AUC, Cmax, Cmin, as appropriate) and selected PD measures (e.g. serum IGF-1, GH, and GHBP levels).

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.

3.7.4 Immunogenicity (IM) Analysis

Samples collected at pre-dose on Days 1, 29, 57, 85, and 112, and anytime on Day 127, 141, 155, 183, and 211, including early termination samples for IM assessment may be analyzed for anti-ISIS 766720 antibodies (ADA). However, plasma samples collected at other time points (for PK purposes) may also potentially be evaluated if deemed of further interest and warranted by the pharmacokinetic scientist. An evaluable sample will be designated 'IM positive' based on both positive screening and confirmation assay results (i.e., confirmed positive result), and otherwise will be deemed 'IM negative'. Sample IM results (screen positive/negative, confirmed positive/negative or unevaluable, and when applicable, titer of anti-ISIS 766720 antibodies) before, during, and after treatment with study drug (ISIS 766720 or placebo) (sample IM status) will be listed by treatment and dose.

Study patients will be given 'IM positive' status if they have at least one confirmed positive sample result at any time during the treatment or post-treatment evaluation periods. Study patients will be given 'IM negative' status if all evaluated IM sample results during the treatment and post-treatment evaluation periods are IM negative and they have at least one evaluable IM result collected post study drug treatment. Otherwise, a study patient will be given 'unknown' IM status. Patient IM results will be listed by treatment and dose for all evaluable patients, which will include but may not be limited to: patient IM status (positive, negative or unknown), 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}), the time of last evaluable IM sample collected ($T_{last\ sampling}$), peak titer, and time to reach peak titer. The onset of ADA and time to reach peak titer will be calculated by:

- Onset in days = The date of first sample has "positive" sample IM status - first dose date +1;
- Time to reach peak titer in days = The date of first peak titer observed- first dose date +1;

Other immunogenicity data analysis (e.g. classification as transient or persistent status for IM positive patients) may be conducted if there are sufficient number of patients with transient IM status. Transient and Persistent ADA definitions are defined below and based on Shankar et al. (2014).

Transient ADA response will be defined as:

- Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point, which will be considered persistent unless shown to be undetectable at a later time) or
- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the patient's last sampling time point is ADA-negative.

Persistent ADA response will be defined as:

- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer or
- Treatment-induced ADA detected only at the last sampling time point of the study treatment period or at a sampling time point with less than 16 weeks before an ADA-negative last sample.

The sample IM incidence (number) and incidence rate (percent) at each evaluated study time point, and for the overall treatment and post-treatment evaluation period, as well as patient IM incidence and incidence rate, will be determined and appropriately summarized by treatment, as the total number of and percentage of evaluated patients with IM negative, positive, and unknown status. Patients with positive IM status may further be classified as transient or persistent status if applicable, and incidence and incidence rate for being transient or persistent will be appropriately summarized. Furthermore, onset, titer over time, and peak titer of the ADA response, if applicable, will be also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%), and range and presented graphically, if deemed appropriate, by treatment at the discretion of the designated study pharmacokineticist and/or statistician (e.g., summarized at each evaluated study time point and overall; summarized by observed peak titer values from the individual IM positive patients; etc.).

In addition to PK assessments (Section 3.7.2), selected safety (Section 3.8) and efficacy (Sections 3.6) assessments may be further stratified by patient IM status (i.e., patient IM status being positive, negative or unknown) and presented in tables and/or graphically, as deemed appropriate or warranted by the designated study pharmacokineticist, medical monitor, and/or biostatistician. Other stratifications (e.g., based on antibody titer, onset of ADA, etc.) of selected PK, efficacy and safety assessments may also be performed if deemed warranted at the discretion of the pharmacokineticist, medical monitor, and/or biostatistician.

3.8 Safety Analyses

The safety analysis will be conducted on the Safety Set.

3.8.1 Exposure

Treatment duration and amount of Study Drug (ISIS 766720 or placebo) received will be summarized by treatment group. The treatment duration for each subject is defined as last dose date - first dose date +1.

3.8.2 Adverse Events

The incidence of AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 (or higher) preferred term and system organ class (SOC) for:

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

SAEs and non-serious AEs that lead to study discontinuation or investigational drug discontinuation will be listed separately. Non-treatment emergent adverse event will be flagged in the data 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 <u>before</u> first dosing, and the second AE record occurs <u>after</u> 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 <u>after</u> 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.

The most conservative approach will be used to determine if the event occurs after the treatment. For example, if the onset date or resolution date of an AE is prior to the first study treatment date, it will be considered to have occurred prior to the study period. If the onset or resolution date of an AE is a partial date with only month or year available or complete missing, then the event is assumed to be within the study period unless the year is prior to the year of the first study treatment date, or if in the same year, the month is prior to the month of the first study treatment date.

3.8.2.1 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 pruitus, 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 injection site is the principal reason for discontinuation.

Percentage of injections leading to local cutaneous reaction at the injection site will be calculated as follows for each subject: (A/B)*100, where A=number of injections with a 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.

3.8.2.2 Flu-like Reactions

Flu-like reactions will also be summarized by preferred term.

Flu-like reactions are defined as either (A) flu-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, and 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 the 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.

3.8.2.3 AE of special interest (AESI)

Per protocol, severe reductions in platelet count < 50,000/mm3 accompanied by a clinically-relevant bleeding event or platelet count of < 25,000/mm3 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 by preferred term. A listing of AESI will also be generated.

3.8.3 Laboratory Measurements

Bone biomarkers, pituitary axis, thyroid panel, inflammatory, lipid panel, chemistry, hematology, coagulation, complement and urinalysis (result, change and percent change from baseline) will be summarized by treatment group and each post-baseline visit.

For ALT and AST, the number and percent of subjects falling in each of the following categories will be tabulated by treatment group:

- ALT/AST > 3 x ULN, confirmed
- ALT/AST > 5 x 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 that value is in the same or worse category then the initial value is confirmed. If the consecutive value is in a better category then the initial value is confirmed using the consecutive value category. If there is no retest within 7 days 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 100,000mm^3 to lower limit of normal
- Confirmed Platelet count 75,000 to < 100,000mm^3
- Confirmed Platelet count 50,000 to < 75,000mm^3
- Confirmed Platelet count 25,000 to < 50,000mm^3
- Confirmed Platelet count < 25,000mm^3
- Confirmed ≥ 30% Platelet count decrease from baseline

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

3.8.4 Vital Signs

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

3.8.5 12-Lead Electrocardiograms (ECG)

Safety 12 lead ECG will be performed in triplicate at the visits indicated in the protocol Schedule of Procedures. The baseline is defined as the average of the triplicate prior the first dose of study drug.

The ECG data will include ventricular rate (VR), PR interval, QRS duration, QT, QTcF (QT corrected using the Fridericia's formula), and QTcB (QT corrected using the Bazett's formula). QTcF and QTcB will be calculated based on the subject's reportable ECG data at each time point using the formula described below:

$QTcF = QT / (RR)^{1/3}$, where RR= 60/VR

$QTcB = QT / (RR)^{1/2}$, where RR= 60/VR

Only calculated QTcB and QTcF will be summarized and included in the data listing. The QTcB and QTcF values recorded on the CRF will not be summarized and will be excluded from the data listing.

For the continuous variables above, descriptive statistics (n, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum and maximum) of the average of triplicate 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 worst of triplicate results at each visit will be summarized by counts and percentages. All the ECG data collected in triplicate, except the CRF QTcB and QTcF values, will be listed.

3.8.6 Acromegaly Past Medications and Concomitant Medications

Acromegaly Past Medications and concomitant medications will be coded using WHO Drug dictionary (version March 2018) and summarized by ATC class, generic name and treatment group.

4 REFERENCES

1) "**Acromegaly Quality of Life Questionnaire (AcroQoL) User's Manual.**" Version: August 2017.
2) "**Acromegaly Quality of Life Questionnaire (AcroQoL).**" Xavier Badia, Susan M Webb, Luis Prieto and Nuria Lara. ***Health and Quality of Life Outcomes*** *2004,* 2:13
3) G Shankar et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations AAPS J. 2014 Jul;16(4):658-73.