Statistical Analysis Plan for Interventional Studies

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I confirm that I have reviewed this document and the accompanying TFL shells and agree with the content.

Approvals

Syneos Health Approval

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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
BID	Twice daily
BLQ	Below the limit of quantification
BMI	Body Mass Index
CAS	Clinical Activity Score
COVID-19	Coronavirus Disease 2019
CMH	Cochran-Mantel-Haenszel
CSS	Clinical Severity Score
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic Case Report Form
GGT	gamma-glutamyl transferase
GO-QoL	Graves Ophthalmology Quality of Life
HbA1c	Hemoglobin A1c
HBsAg	hepatitis B surface antigen
HEENT	Head, eyes, ears, nose, and throat
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICH	International Council for Harmonization
IGF-1	Insulin-like Growth Factor
IGF-1R	Insulin Growth Factor-1 Receptor
Phospho-IGF-1R	Phospho-insulin Growth Factor-1 Receptor
ITT	Intent to Treat
IUD	Intrauterine Devices
LDH	Lactate Dehydrogenase
MAR	Missing-at-random
MCMC	Markov Chain Monte Carlo
MDRM	Masked Data Review Meeting
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model Repeated Measures
NCA	Non-compartmental Analysis
NCI	National Cancer Institute
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per Protocol
PT	Preferred Term
QTcF	QT interval corrected using the Fridericia method
RANTES	Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvate transaminase

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Abbreviation	Description
SI	Standard International
SOC	System Organ Class
SOP	Standard Operating Procedure
TED	Thyroid Eye Disease
TEAE	Treatment-emergent AE
TFL	Tables, Figures and Listings
Tg	Thyroglobulin
TPO	Thyroperoxidase
TSH	Thyroid-stimulating Hormone
TSHR	Thyroid-stimulating Hormone Receptor
TSHRAbs	Thyroid-stimulating Hormone Receptor Autoantibodies
ULN	Upper Limit of Normal
WHO	World Health Organization

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2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. Mock TFL shells are included in a separate document. A TFL index is also provided in a separate document.

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

A Data Safety Monitoring Board (DSMB) is planned for this study. A separate DSMB Charter will detail the frequency of meetings, members, and the safety review criteria to be assessed. The DSMB will review descriptive summaries of subject disposition, subject characteristics, and safety data. The tables, figures and listings (TFLs) that will be provided to the DSMB are detailed in the TFL index. Each DSMB meeting will consist of an open session and closed session. In the open session, only masked TFLs will be presented. In the closed session, unmasked data will be presented. See Section 4.4 for details regarding production of masked and unmasked TFLs for the DSMB.

There will be a data 'freeze' after all subjects have had their week 24 visit. At this stage unmasking will occur. The 'main' analysis for the study will be conducted at this stage. A set of topline TFLs will be expedited.

A 'follow-up' analysis will be conducted after all follow-up data to week 72 has been collected , where an updated version of all TFLs which use any data beyond the week 24 visit will be provided. An 'extended follow-up' analysis will be conducted after all extended follow-up data to week 120 has been collected, where an updated version of all TFLs which use any data beyond the week 72 visit will be delivered.

The TFLs that will be delivered at each analysis (DSMB, topline, week 24, week 72 and week 120) are described in the TFL index.

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3. Study Objectives

3.1. Primary Objective

The primary objective is to study the effect of two doses of linsitinib versus placebo on the proptosis responder rate at Week 24. Responder rate is the percentage of subjects with a ≥ 2 mm reduction from Baseline in the primary study eye without deterioration (≥ 2 mm increase) of proptosis in the contralateral non-study eye.

3.2. Secondary Objective(s)

1. Evaluate the effect of linsitinib versus placebo on the mean change from Baseline to Week 24 in proptosis measurement in the primary study eye.
2. Evaluate the effect of linsitinib versus placebo on the overall responder rate (percentage of subjects with ≥ 2-point reduction in 7-point Clinical Activity Score (CAS) and ≥ 2 mm reduction in proptosis from Baseline, provided there is no corresponding deterioration (≥2-point mm increase) in CAS or proptosis in the contralateral non-study eye at Week 24.
3. Evaluate the effect of linsitinib versus placebo on the percentage of subjects with a CAS value of 0 or 1 at Week 24 in the primary study eye.
4. Evaluate the effect of linsitinib versus placebo on the mean change from Baseline to Week 24 in the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire overall score.

3.3. Exploratory Objective(s)

1. Evaluate the effect of linsitinib versus placebo on the Clinical Severity Score (CSS) individual response status frequencies and percentage of responders for each component of clinical severity from Baseline to Week 24.
2. Evaluate the effect of linsitinib versus placebo on the mean change from Baseline to Week 24 in the CAS.
3. Evaluate the effect of linsitinib versus placebo on the overall responder rate at Week 24 stratified by the level of response (high responders, responders, low responders, and non-responders).
    - Stratification of Proptosis and CAS Response into Four Responses Categories
    - To further explore the response based on both proptosis and CAS reduction, each subject will be classified into one of 4 response categories at Week 24:

[Proprietary responder-classification thresholds redacted - confidential]

    - A logistic regression analysis will be used to compare the treatment groups on the basis of this ordered 4-category classification.

4. Evaluate pharmacokinetic (PK) parameters of linsitinib to estimate exposure and understand PK-pharmacodynamic (PD) relationships.
5. Evaluate the effect of linsitinib versus placebo on the mean change from Baseline to Week 24 in the GO-QoL questionnaire visual functioning (VF) and appearance (A) subscale scores.
6. Evaluate the effect of linsitinib on the mean change from Baseline to Week 24 in blood and serum biomarkers.
7. Evaluate the effect of linsitinib versus placebo on the mean change from Baseline to Week 24 on the motility component of the CSS.
8. Evaluate the effect of linsitinib versus placebo on the diplopia responder rate (i.e., the percentage of subjects with Baseline diplopia > 0 in the primary study eye who have a reduction of ≥ 1 grade with no corresponding deterioration [≥1 grade worsening] in the contralateral non-study eye) at Week 24

3.4. Safety Objective

1. To assess the safety and tolerability of linsitinib as compared to placebo over a 24-week period.

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4. Study Details/Design

4.1. Brief Description

This is a phase 2b, double-mask, randomized, placebo controlled, multicenter, efficacy, safety and tolerability, PK, PD trial of linsitinib. Study drug is administered twice daily for six-months (24 weeks) in approximately 75 men and women (25 will be randomized to placebo) with active, moderate to severe TED.

Subjects will be screened for the study within 2 to 4 weeks prior to the Baseline (Day 1) Visit. Approximately 75 subjects (25 per group) who meet the study eligibility criteria will be randomized on Day 1 in a 1:1:1 ratio to receive either 75 mg BID linsitinib (n=25), 150 mg BID linsitinib (n=25) or placebo BID (n=25). All subjects will enter a 24-week Double-mask Treatment Period, during which study drug will be administered on Day 1 (Baseline), and twice daily through Week 24. Clinic study visits will occur at Baseline, Weeks 3, 6, 9, 12, 15, 18, 21, and 24.

At the end of Treatment Period (Week 24), subjects in whom the primary study eye has < 2 mm decrease in proptosis (proptosis non-responders) will be have the option to enter an Extension Study (VGN-TED-302). Specifically, proptosis non-responders on placebo during the Treatment Period will be randomized to receive either 75 mg BID or 150 mg BID linsitinib. Proptosis non-responders randomized to linsitinib during the Treatment Period will continue on the linsitinib dose they were randomized to during the Treatment Period. All subjects will be masked to an active study medication dose.

At Week 24, subjects in whom the primary study eye has ≥ 2 mm decrease in proptosis (proptosis responders), as well as proptosis non-responders, who choose not to enroll in the extension study (VGN-TED-302), will enter a 48-week Follow-up Period, during which study drug will not be administered and clinic visits are scheduled for Weeks 28, 36, 48, 60, and 72. Subjects considered proptosis responders at Week 24 who relapse at any time during the 48-week Follow-up Period will have the option to enroll in VGN-TED-302 if they meet all criteria.

Subjects who prematurely discontinue study drug dosing at any time prior to completion of the 24-week clinic visit will return to the clinic and undergo the scheduled Week 24 assessments and will be encouraged to participate in the Follow-up Period unless they initiated another intervention due to lack of efficacy. Subjects who enter the Follow-up Period but prematurely discontinue study at any time prior to completion of the Week 72 clinic visit will return for a final visit and undergo the scheduled Week 72 assessments prior to study discharge.

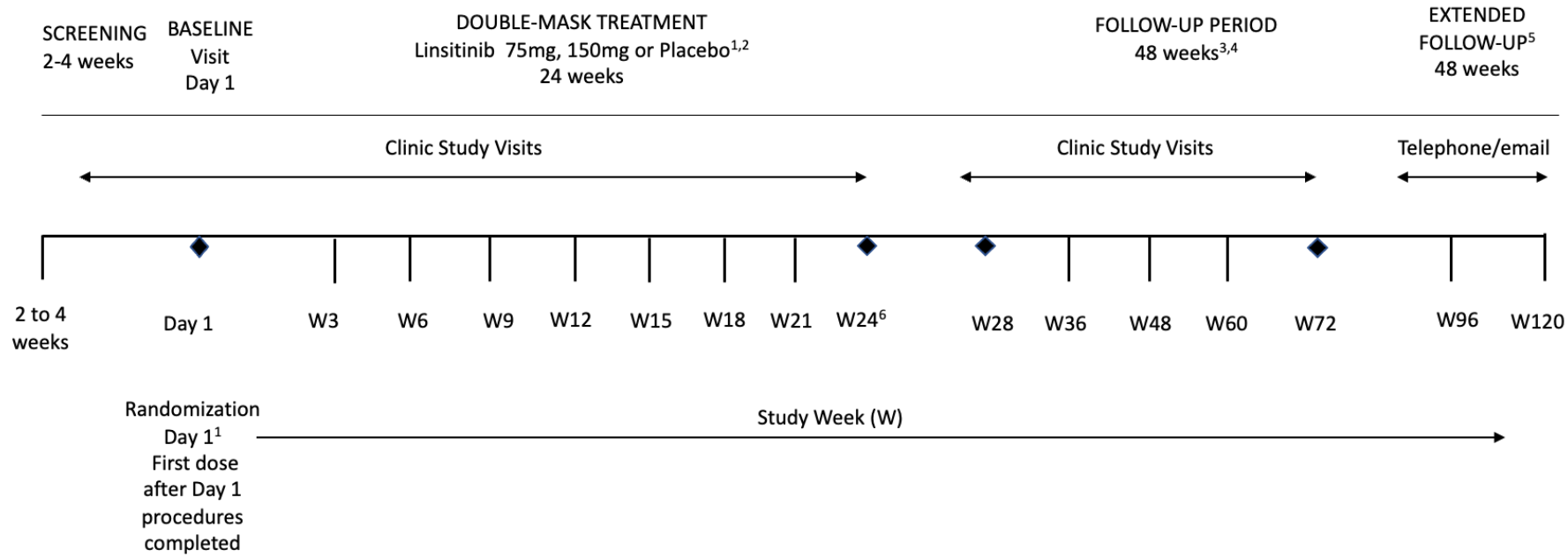
Subjects who complete the Week 72 Visit will be contacted by email or phone 6 and 12 months later to determine if any treatment has been received for TED since last contact by study team. If treatment has been rendered, the subject will be asked to provide details on the type of treatment and associated outcomes.

A study design overview is presented in the schematic below. Detailed study activities are provided in Table 1.

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Figure 1: Study Schematic



[1]Subjects will be randomized in a 1:1:1 ratio to receive: linsitinib 75 mg BID or 150 mg BID or Placebo BID

[2]Visit windows are ± 3 days for Day 1, Weeks 3, 6, 9, 12, 15, 18, 21, and 24.

[3]At Week 24, responders will enter a 48-week Follow-up Period, during which study drug will not be administered.

[4]Visit windows of ± 7 days.

[5]Subjects who complete the Week 72 Visit will be contacted via phone or email by research staff at Week 96 and Week 120 to enquire if any treatment for TED has been received since last study contact.

[6]After completion of Week 24 of the Double-mask Treatment Period, the following subjects will be invited to enroll into VGN-TED-302 to receive study treatment:

-Subjects who are proptosis responders but relapse during the Follow-up Period.: Relapse subjects will receive the same dose they received during the treatment period.

-Subjects who are proptosis non-responders: Proptosis non-responder placebo subjects will be randomized to receive either 75 mg BID or 150 mg BID linsitinib. Proptosis non-responder linsitinib subjects will receive the same dose they received during the Double-mask Treatment Period.

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Table 1: Schedule of Activities

Study Period	Screening	Baseline/ Randomization	Double-mask Treatment Period								Follow-up Period					301 Ext Follow-Up	
Visit	S1[1]	Baseline	W3	W6	W9	W12	W15	W18	W21	W24/ EOT	W28	W36	W48	W60	ET W72	W96	W120 /EOS
Day(s)	-28 to -14	Day 1	22	43	64	85	106	127	148	169	197	253	337	421	505	673	841
Study Visit Window		(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 3)	(± 7)	(± 7)	(± 7)	(± 7)	(± 7)	(± 7)	(± 7)
Informed Consent	X																
Inclusion/Exclusion	X	X															
Demographics, including smoking and childbearing status	X																
Medical and Surgical History	X																
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test - serum[2]	X																
Urine Pregnancy Test		X	X	X	X	X	X	X	X	X	X						
Physical Exam	X	X		X		X		X		X			X		X		
Vital Signs, Height[3], Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pretibial Myxedema Exam		X								X					X		
Ophthalmologic exam[4]	X	X		X		X		X		X	X	X	X		X		
ECG (Electrocardiogram)/QT Evaluation[5]	X	X[5]	X[5]	X	X	X	X	X	X	X	X	X	X	X	X		
Hematology - CBC + Differential[6]	X	X	X	X	X	X	X	X	X	X		X			X		
Hemoglobin A1C	X					X				X		X			X		
Blood Glucose[7]	X	X	X	X	X	X	X	X	X	X		X			X		
Chemistry Panel[8]	X	X	X	X	X	X		X		X		X			X		
Cotinine	X																
Urinalysis[9]	X	X	X	X	X	X		X		X		X			X		
Metabolic Thyroid Function (FT4, FT3, TSH)	X	X		X		X		X		X		X			X		
Viral Screen Human immunodeficiency virus (HIV), Hep B, Hep C)	X																

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Randomization via IRT and First Dosing		X															
Dispense study drug		<----------->[12]															
Drug Reconciliation			<----------->[12]														
CAS [10]	X	X		X		X		X		X	X	X	X	X	X		
CSS including proptosis, diplopia, and motility restriction	X	X		X		X		X		X	X	X	X	X	X		
GO-QOL		X		X		X				X	X		X		X		
PK - Day 1 (pre-dose and hours 2, 3 and, 4 post-dose), Week 3 (pre-dose and hours 2, 3, and 4 post-dose), Week 6 (pre-dose and 2 hr post-dose[11]), Week 15 (pre-dose), Week 24 (pre-dose)		X	X	X			X			X							
PD – Day 1 (pre-dose and 4 hr post-dose), Week 3 (pre-dose), Week 15 (pre-dose), Week 24 (pre-dose), and Week 36		X	X				X			X		X					
Adverse Events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TED Treatment Phone/Email Evaluation																X	X

End of Treatment EOT, End of Study EOS, Early Termination (ET)

[1]Screening period is 2-4 weeks prior to Baseline Visit. Subjects who have a ≥ 2 mm decrease in proptosis in the primary study eye from Screening are not eligible for randomization. All laboratory assessments at Screening are to be fasted.

[2]Pregnancy test is for women of childbearing potential including those with an onset of menopause <2 years prior to Screening, non-therapy-induced amenorrhea for <12 months prior to Screening, or not surgically sterile [absence of ovaries and/or uterus]). Serum test at screening only. Urine test at all other visits unless positive, in which serum would be required for follow-up.

[3] Body mass (BMI) and height at screening only

[4]Ophthalmic exam: best corrected visual acuity, pupil exam, color vision assessment, (Ishihara color plates (or equivalent) or related red desaturation), intraocular pressure, and slit lamp exam. If significant abnormalities are noted compared to previous visits, including a loss of 2 lines or more of vision, development of pupil abnormalities including APD, rise in intraocular pressure, development of corneal infiltrates or other abnormalities not here specified but of concern to the ophthalmologist, further investigations of visual function will be conducted according to the ophthalmologist decision.

[5]Prior to performing any ECG, subjects should rest in the supine position for at least 5 minutes. All ECGs should be recorded digitally and in triplicate (repeated 3 times at least 1 minute apart). The mean QTcF of the triplicate ECG tracings should be used for all treatment decisions. Day 1 and Week 3 will have ECG at pre-dose, and hours 2, 3, and 4 post-dose. The subsequent visits at 3-week intervals will require one triplicate ECG (starting at Week 6 visit). Hourly ECG measurements should be performed with a window of +/- 5 minutes.

[6]Fasting total cholesterol, and triglyceride values at Screening only for all subjects. All subsequent visits are either fasted or non-fasted depending on the subject's diabetic status.

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[7] Diabetic subjects will have fasting glucose at every study visit. Non-diabetic subjects will have fasting glucose at Screening and Baseline/Day1 and non-fasting glucose for subsequent visits.
[8] Alanine Aminotransferase (ALT)/ Aspartate Aminotransferase (AST) must be ≤ 3 x the ULN and serum creatinine must be < 2 x the ULN according to age for randomization
[9]If urine ketones are considered clinically significant, blood ketones, lactate, and/or bicarbonate should be collected
[10]CAS must be ≥ 4 for enrollment and randomization, subjects whose CAS score decreases 2 or more points in the primary study eye from Screening are not eligible for randomization.
[11] One or two subjects enrolled at each site will have an additional PK sample collected at 2 hours post-dose on at Week 6
[12]Arrows indicate drug dispensing and reconciliation. For more detailed information, please see the Pharmacy Manual.

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4.2. Subject Selection

The planned number of subjects is 75.

4.2.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation:

1. Subjects must be ≥18 years of age at Screening.
2. Clinical diagnosis of Graves' Disease and/or autoimmune Hashimoto's thyroiditis associated with active moderate to severe TED with a CAS ≥ 4 (on the 7- item scale) for the most severely affected eye (primary study eye) at Screening and Baseline.
3. Moderate-to-severe active TED (not sight-threatening but has an appreciable impact on daily life), with diagnosis of TED within 12 months prior to the Screening visit and usually associated with one or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, exophthalmos ≥ 3 mm above normal for race and gender, and/or inconstant or constant diplopia. An additional period of 4 weeks will be permitted beyond the 12 months for the purposes of washing out any prohibited medications or supplements if needed.
4. Subjects must be euthyroid with the participants baseline disease under control or have mild hypo- or hyperthyroidism (defined as free thyroxine (FT4) and free triiodothyronine levels (FT3) <50% above or below the normal limits at Screening. Every effort should be made to correct mild hypo- or hyperthyroidism promptly and maintain the euthyroid state for the duration of the clinical trial.
5. Does not require immediate ophthalmic surgery, radiotherapy to orbits or other ophthalmological intervention at the time of Screening and is not planning for any such treatment during the course of the study.
6. Diabetic subjects must have HbA1c < 9.0%. Type 2 diabetic subjects who are not on insulin, must not be prescribed insulin within 60 days prior to screening. If Type 1 or Type 2 diabetic subjects are on insulin, the prescribed total daily insulin dose must not have changed by more than 20% or more than 10 units (whichever is greater) in the 60 days prior to Screening. Subjects must have no severe hypoglycemic events (requiring medical care by health care professional) in the 60 days before screening.
7. Women of childbearing potential (WOCBP) are required to have a negative serum pregnancy test at time of Screening and a negative urine pregnancy test at each timepoint that is specified in protocol. The definition of childbearing potential also includes women with the onset of menopause <2 years prior to Screening, women with non-therapy-induced amenorrhea for <12 months prior to Screening, and women who are considered infertile (sterile) from non-surgical conditions [absence of ovaries and/or uterus]). These women are also required to have a negative serum pregnancy test at time of Screening and a negative urine pregnancy test at each timepoint that is specified in protocol. Women who are sexually active with non-vasectomized male partners must agree to use 2 reliable forms of contraception from Screening through the treatment phase of the trial and for 28 days following the last dose of the study drug. It is recommended that hormonal (i.e.: oral contraceptive) contraception be one of these contraceptive methods used. Hormonal contraception must be initiated ≥ 21 days prior to Baseline visit and continue for 28 days following the last dose of study drug. When used correctly and consistently, highly effective contraceptive methods including combined oral contraceptives, some intrauterine devices (IUDs), injectables, implants, sexual abstinence or sex with a vasectomized partners have a failure rate < 1% per year. Women must agree to and refrain from donating ova during the study, and for 28 days after receiving the last dose of study drug.
8. Male subjects who are sexually active with a female partner of childbearing potential (as defined

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above), must agree to use barrier contraceptive method from Screening through 75 days after the last dose of study drug. Otherwise, sexually active male subjects must be surgically sterile. Men must agree to and refrain from donating sperm during the study, and for 75 days (90 in the UK) after receiving the last dose of study drug.

9. Subject is willing and able to sign written informed consent and comply with the protocol for the duration of the study.

4.2.2. Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 2 lines on the Snellen chart, new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months.
2. Corneal decompensation unresponsive to medical management.
3. Decrease in CAS of ≥ 2 points in the primary study eye between Screening and Baseline.
4. Decrease in proptosis of ≥ 2 mm in the primary study eye between Screening and Baseline.
5. Previous orbital irradiation or orbital surgery.
6. Prior IGF-1R inhibitor therapy for any condition.
7. Any glucocorticoid use (intravenous [IV] or oral) with a cumulative dose equivalent to ≥ 1g of methylprednisolone or equivalent for the treatment of TED within 3 months of Screening. Previous glucocorticoid use (IV or oral) with a cumulative dose of <1g methylprednisolone or equivalent for the treatment of RED and previous use of steroid eye drops is allowed if discontinued at least 4 weeks prior to Screening.
8. Any glucocorticoid use for conditions other than TED within 4 weeks prior to Screening (topical steroid for dermatological conditions and inhaled steroids are allowed)
9. Use of any non-steroid immunosuppressive agent within 4 weeks prior to Screening.
10. Any previous treatment with anti-IL6 receptor, anti- CD20, (MS4A1) antibodies or monoclonal antibody for immunomodulation.
11. Selenium and/or biotin use within 3 weeks prior to Baseline is disqualifying, not allowed and must not be restarted during the clinical trial or Follow-up period. However, taking a multivitamin containing selenium and/or biotin is permitted.
12. Use of an investigational agent for any condition within 30 days prior to Screening or anticipated use during the course of the trial.
13. Under no circumstances are subjects who have enrolled in this study permitted to be re-randomized to this study. Note: Prior to enrollment subjects who have failed screening may be allowed to rescreen after consultation with the Medial Monitor.
14. Identified pre-existing ophthalmic or other disease that in the judgement of the Investigator, would preclude study participation or complicate interpretation of study results (e.g. including, but not limited to: previous eyelid surgery, corneal disease [other than keratopathy caused by TED that does not meet any other exclusion], uveitis, diabetic macular edema, diabetic retinopathy, retinal vein occlusion, macular degeneration, other retinopathy, retinal detachment, glaucoma, or optic nerve disease or optic nerve injury).
15. Ocular surgery other than routine cataract surgery, subsequent YAG laser capsulotomy and corneal refractive surgery. (Cataract surgery, YAG laser capsulotomy and corneal refractive surgery are allowed if the surgical procedure(s) were performed more than 3 months prior to randomization).
16. Biopsy-proven or clinically suspected inflammatory bowel disease (e.g., diarrhea with or without blood or rectal bleeding associated with abdominal pain or cramping/colic, urgency, tenesmus, or

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incontinence for more than 4 weeks without a confirmed alternative diagnosis OR endoscopic or radiologic evidence of enteritis/colitis without a confirmed alternative diagnosis).

17. History of QTcF prolongation; or QTcF prolongation at Screening; mean QTcF interval > 450 msec (males); and > 470 msec (females).
18. Use of drugs potentially associated with causing QT interval prolongation within 14 days prior to Day 1 dosing. A resource that provides a comprehensive list of medications that may have a risk of QT prolongation can be found at https://www.crediblemeds.org/index.php/druglist.
19. ALT or AST > 3 times the upper limit of normal (ULN) according to age at Screening.
20. Serum creatinine > 2 x ULN for the reference range laboratory according to age at Screening.
21. Malignant conditions being actively treated or treated in the past 12 months (with the exception of successfully treated basal cell of the skin). Recent (within 3 months of Screening) basal cell of the eyelid skin is excluded.
22. Pregnant or lactating women.
23. Current drug, marijuana or alcohol abuse, or history of either within the past 1 year, in the opinion of the Investigator, or as reported by the subject.
24. In the opinion of the Investigator, any conditions which may pose increased risk of participation for the subject or may interfere with interpretation of study results.
25. Uncontrolled Human immunodeficiency virus (HIV), as judged by the Investigator, hepatitis C, or hepatitis B.

4.3. Determination of Sample Size

Assuming approximately a 10% screen failure rate, and a 10% discontinuation rate before Week 24, 75 total enrolled subjects will provide a minimum of 22 evaluable subjects per each of the three arms, providing data at Week 24. Assuming a placebo [Redacted] and the higher efficacious dose at a [Redacted] success rate, there is [Redacted] for a given linsitinib dose arm with alpha (1-sided) = 0.025 for a given linsitinib dose arm.

4.4. Treatment Assignment and Masking

The study is randomized in order to minimize bias in determining which subject receives which dose of linsitinib, or placebo.

Following Baseline procedures, eligible subjects will be assigned a randomization number and corresponding treatment. Subjects will be randomized to receive either 75 mg BID or 150 mg BID linsitinib or placebo BID (n=25 per group) and given study medication and daily dosing instructions. The randomization scheme is 1:1:1 (75 mg BID linsitinib:150 mg BID linsitinib: placebo BID). There are no randomization stratification factors.

Under no circumstances are subjects who have enrolled in this study permitted to be re-randomized to this study. Changes in treatment are not permitted following randomization.

This study is double-masked so there is no bias introduced by knowledge of the treatment identity received by a subject reporting a clinical finding. Double masking also minimizes the bias in assessing treatment response measures that could be introduced by the Investigators had they known the treatment identity.

The randomization list will be kept in a secure location until after unmasking. However, the treatment assignment for an individual subject will be provided if unmasking is necessary for a serious adverse event (SAE).

Unmasking will occur after a data 'freeze' after all subjects have had their 24-week visit.

A DSMB is planned for this study. The DSMB will advise the Sponsor whether to continue, modify, or stop a trial for the continuing safety of the study subjects and potential subjects as well as continuing validity and scientific merit of the trial. A separate DSMB Charter will detail the frequency of meetings, members, and the safety review criteria to be assessed. The DSMB shall have written procedures and maintain records of all its meetings.

Throughout the masked portion of the study, masked TFLs will be produced as required by the masked Biostatistical team by using the dummy randomization list for treatment assignment. As such, TFLs will be presented exactly as per the TFL shells, but each presented treatment group will consist of a random mixture of all treatment groups. In order to produce unmasked TFLs for the DSMB throughout the masked portion of the study, a separate unmasked Biostatistical team will undertake analyses in a secure area using programs developed by the masked team but utilizing the actual randomization list (also stored in a secure area), so that the presented treatment groups reflect the true treatment assignment.

4.5. Administration of Study Medication

Subjects will receive twice daily doses of linsitinib or matching placebo for 24 weeks, according to the treatment group they are assigned. Study drug will be administered on site on Day 1.

All treatments should be administered in the morning, and in the evening approximately 12 hours apart with food and approximately 240 mL of water.

If a subject misses a dose of study drug, the subject may take the missed dose at any time up to 6 hours before the next intended dose. Subjects will be instructed to notify study site personnel of any missed doses.

Dosing on Weeks, 3, 6, and 15 will be done in the clinic after blood draws. Subjects should not take their morning dose of study drug at home prior to these visits. Instead, they will be directed to take their medication after pre-dose PK blood draws are completed while in clinic.

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5. Endpoints

The more severely affected eye will be defined as the primary study eye at the Baseline (Day 1) Visit. If both eyes meet eligibility requirements and there is a discrepancy between CAS and proptosis in determining the primary study eye, then this will be adjudicated always to the eye with the more significant proptosis. If both eyes are affected equally, the Investigator will choose the primary study eye. Both eyes will be assessed for efficacy, but the primary study eye will be used to assess the primary outcome measure.

5.1. Primary Efficacy Endpoint

Rate of effect of linsitinib versus placebo on the proptosis responder rate at Week 24. Responder rate is the percentage of subjects with a ≥ 2 mm reduction from Baseline in the primary study eye without deterioration (≥ 2 mm increase) of proptosis in the contralateral non-study eye.

5.2. Secondary Efficacy Endpoints

If the primary hypothesis is met, secondary endpoints will be tested in a hierarchical manner (in the order that follows), for all doses that met the primary endpoint compared to placebo.

1. Mean change from Baseline to Week 24 in proptosis measurement in the primary study eye.
2. Overall responder rate (percentage of subjects with ≥ 2-point reduction in CAS and ≥ 2mm reduction in proptosis from Baseline, provided there is no corresponding deterioration (≥2-point/ mm increase) in CAS or proptosis in the contralateral non-study eye at Week 24.
3. Percentage of subjects with a CAS value of 0 or 1 at Week 24 in the primary study eye.
4. Mean change from Baseline to Week 24 in the GO-QoL.

5.3. Exploratory Endpoints

1. CSS individual responses for each component of clinical severity from Baseline to Week 24.
2. Mean change from Baseline to Week 24 in the CAS.
3. Overall responder rate at Week 24 stratified by the level of response (high responders, responders, low responders, and non-responders). See Section 10.3 for details.
4. Mean change from Baseline to Week 24 in the GO-QoL questionnaire visual functioning (VF) and appearance (A) subscale scores.
5. Mean change from Baseline to Week 24 in blood and serum biomarkers.
6. Mean change from Baseline to Week 24 on the motility component of the CSS.
7. Diplopia responder rate (i.e., the percentage of subjects with Baseline diplopia > 0 in primary study eye who have a reduction of ≥ 1 grade with no corresponding deterioration [≥1 grade worsening] in the contralateral non-study eye at Week 24.

5.4. Safety Endpoints

- AEs / SAEs
    - Treatment-emergent AEs (TEAEs; defined as AEs that begin or worsen after the first dose of study drug)
    - Treatment-emergent SAEs
    - Deaths
    - Discontinuation due to AEs

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- Clinical safety laboratory results
- Vital signs
- Physical examination
- ECG parameters

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6. Analysis Populations

6.1. Enrolled Population

The Enrolled Population will include all subjects. Unless otherwise specified, this set will be used for summaries of screen failures, unmet eligibility criteria, informed consent, exclusions from analysis populations and protocol deviations.

6.2. Intent to Treat (ITT) Population

The ITT Population will include all subjects randomized and will be assessed as randomized. The ITT population will be used for summaries of subject disposition, demographics and baseline characteristics, as well as efficacy analyses.

6.3. Per Protocol (PP) Population

The PP Population will include all randomized subjects without important protocol deviations (protocol deviations which are considered to potentially bias efficacy results). This population will be used in selected sensitivity analyses for efficacy endpoint.

Deviations which are considered to be important enough to warrant exclusion from the PP population will be determined prior to week 24 data freeze (and therefore prior to unmasking) at a masked data review meeting (MDRM). During this meeting, a comprehensive medical review of masked subject data (e.g., via listings) will be undertaken in order to determine exclusions from analysis populations that cannot be performed programmatically, including the PP population. Meeting attendees will include (but not be limited to), Syneos Health lead Biostatistician, project lead and lead clinical data manager, as well as sponsor representation.

A masked data review plan will be prepared in advance of the MDRM which will outline the scope and format of outputs to be reviewed during the MDRM. The agreed outputs will then be programmed, and review of these outputs will take place during the MDRM. The output from the MDRM will be an analysis sets report, where the exclusions from analysis populations are documented. The final TFLs will then be programmed in accordance with this report.

6.4. Safety Population

The Safety Population (SP) will include all subjects who received at least one dose of study medication. Subjects will be analyzed according to treatment received (based upon first dose of study drug). The SP will be used for all analyses of safety endpoints.

6.5. PK Population

The PK Population will include all subjects who received at least one dose of the study drug and have at least one PK blood sample collected. Subjects who received matching placebo will not be included in the PK population. The PK population will be used for the analysis of PK data.

6.6. PD Population

The PD Population will include all subjects who received at least one dose of the study drug and have at least one PD blood sample collected. The PD population will be used for analysis of exploratory PD endpoints.

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7. Estimands

7.1. Estimands for the Primary Efficacy Endpoint

The **main estimand** for the primary efficacy endpoint 'percentage of subjects with proptosis response at Week 24' is defined by the 5 attributes listed below. Hereby, proptosis response is defined as 'a ≥ 2 mm reduction from Baseline in the primary study eye without deterioration (≥ 2 mm increase) of proptosis in the contralateral non-study eye'.

- Treatment: 75 mg linsitinib or 150 mg linsitinib or matching placebo.
- Population: Of all subjects with Graves' Disease and/or autoimmune Hashimoto's thyroiditis defined by the study inclusion / exclusion criteria, the analysis population will include subjects who were randomized to study treatment (linsitinib versus placebo) (ITT population).
- Variable: Binary variable indicating the treatment response when having completed Week 24 assessment, whereby a responder is defined as a subject who has a ≥ 2 mm reduction from Baseline of proptosis in the primary study eye at Week 24 without deterioration (≥ 2 mm increase) of proptosis in the contralateral non-study eye. This means all subjects with a deterioration of > 2 mm of proptosis in the contralateral non-study eye at Week 24 will be considered as no response or failure, independently of the result observed in the study eye. Missing data at Week 24 will be imputed using multiple imputation of the continuous proptosis variable, using all available prior proptosis measures, smoking status and treatment group. Missing data at screening or day 1 visit will be imputed with the mean value for the corresponding visit across all treatment groups. Both monotone and non-monotone missing data are expected. Thus, any non-monotone missing data will be multiple imputed using a non-monotone Markov Chain Monte Carlo (MCMC) imputation approach. After non-monotone missing data are imputed, monotone missing data will be imputed using a monotone regression approach.
- Population-level summary: Difference in the percentage of treatment responders of linsitinib treatment group versus placebo.
- Intercurrent events:
    - In the event of death, the latest available proptosis observation will be carried forward (i.e., while alive strategy).
    - All other intercurrent events will be treated using the treatment policy strategy, i.e., the assessment of proptosis at Week 24 will be used for the evaluation of response.

A secondary estimand for the primary efficacy endpoint will be as per the main estimand, but subjects receiving a different treatment to which they were randomized will be considered as an intercurrent event. Post treatment initiation, the first instance of receipt of a different treatment to which the subject was randomized will be considered as an intercurrent event. After this point, data will be disregarded and imputed (i.e., hypothetical strategy)

A tertiary estimand for the primary efficacy endpoint will be as per the main estimand, but subjects will be analyzed per treatment received (based upon first dose of study drug).

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7.2. Estimands for the Secondary Efficacy Endpoints

7.2.1. Estimands for the First Secondary Efficacy Endpoint 'Change from Baseline to Week 24 in proptosis measurement in the primary study eye'

The **main estimand** for the secondary efficacy endpoint 'Change from Baseline to Week 24 in proptosis measurement in the primary study eye' is defined by the 5 attributes*:*

- Treatment: as defined in Section 7.1.
- Population: as defined in Section 7.1.
- Variable: Change from Baseline to Week 24 in proptosis measurement in the primary study eye. Missing data at Week 24 will be imputed using similar methods to those described in Section 7.1.
- Population-level summary: Difference between linsitinib versus placebo in the change from Baseline in proptosis measurement in the primary study eye.
- Intercurrent events: as defined in Section 7.1.

7.2.2. Estimands for the Second Secondary Efficacy Endpoint 'Overall Response at Week 24'

The **main estimand** for the second efficacy endpoint 'percentage of subjects with overall response at Week 24' is defined by the 5 attributes listed below. Hereby, overall response is given if a subject with ≥ 2-point reduction in CAS and ≥ 2mm reduction in proptosis at Week 24 from Baseline, does not experience a deterioration (≥2-point/ mm increase) in CAS or proptosis in the contralateral non-study eye.

- Treatment: as defined in Section 7.1.
- Population: as defined in Section 7.1.
- Variable: Binary variable indicating the overall treatment response at Week 24 if subject has ≥ 2-point reduction in CAS and ≥ 2mm reduction in proptosis at Week 24 from Baseline, and does not experience a deterioration (≥2-point/ mm increase) in CAS or proptosis in the contralateral non-study eye. Missing data at Week 24 will be imputed using similar methods to those described in Section 7.1.
- Population-level summary: Difference in the percentage of overall responders of linsitinib treatment group versus placebo.
- Intercurrent events: as defined in Section 7.1.

7.2.3. Estimands for the Third Secondary Efficacy Endpoint 'CAS response at Week 24'

The **main estimand** for the third efficacy endpoint 'percentage of subjects with CAS response at Week 24' is defined by the 5 attributes listed below. Hereby, CAS response is given if a subject has a CAS value of 0 or 1 at Week 24 in the primary study eye.

- Treatment: as defined in Section 7.1.
- Population: as defined in Section 7.1.
- Variable: Binary variable indicating CAS response at Week 24 if a subject has a CAS value of 0 or 1 at Week 24 in the primary study eye. Missing data at Week 24 will be imputed using similar methods to those described in Section 7.1.. Imputed values will be rounded to the nearest integer to determine a value of 0 or 1.
- Population-level summary: Difference in the percentage of CAS responders of linsitinib treatment group versus placebo.
- Intercurrent events: as defined in Section 7.1.

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7.2.4. Estimands for the Fourth Secondary Efficacy Endpoint 'Change from Baseline to Week 24 in the GO-QoL questionnaire overall score'

The main estimand for the secondary efficacy endpoint 'Change from Baseline to Week 24 in the Graves' GO-QoL questionnaire overall score is defined by the 5 attributes*:*

- Treatment: as defined in Section 7.1.
- Population: as defined in Section 7.1.
- Variable: Change from Baseline to Week 24 in GO-QoL assessment. Missing data at Week 24 will be imputed using similar methods to those described in Section 7.1.
- Population-level summary: Difference between linsitinib versus placebo in the change from Baseline in GO-QoL assessment.
- Intercurrent events: as defined in Section 7.1.

8. General Aspects for Statistical Analysis

8.1. General Methods

Unless otherwise specified, summaries will be presented for each treatment. An overall summary will be provided for disposition and baseline information, as well where tables are required to be sorted by the overall count (e.g., event incidence summary tables).

Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), frequency and percentages of subjects.

All relevant subject data will be included in listings.

By-visit summaries will not include rows for unscheduled visits. However, unscheduled visit data will be used in calculation of worst-case post-baseline variables. All unscheduled visit data will be listed. If multiple assessments are made at the same scheduled assessment, the earliest value will be reported in by-visit summaries, with all values listed.

For the purpose of change from Baseline analyses, Baseline is defined as the most recent non-missing measurement prior to the first dose of study drug. This will be the Day 1 measurement, if available and takes place prior to the first dose of study drug. A change from Baseline value is calculated as the post-Baseline value minus the Baseline value. If Day 1 measurements are taken after the first dose of study drug, they will not be considered as the baseline value, and also change from baseline at Day 1 visits will not be considered for analyses.

Week 24 and Week 72 visit data in the CRF is collected in joint records with the EOT and EOS visit, respectively (i.e., 'Week 24/EOT' and 'Week 72/EOS'). As such, for all efficacy and PK analyses, only true Week 24 and Week 72 data will be presented. For safety analyses, true Week 24 and Week 72 data will be presented, in addition to Week 24/EOT and Week 72/EOS, as a summary of last value. Determination of whether records are a true Week 24/Week72 record will be determined by records of early discontinuation of treatment/study.

8.2. Missing Data

Multiple imputation will generally be used for analysis of primary and secondary efficacy endpoints (see Sections 7 and 10 for details). Variables considered in the imputation models will be age, sex and smoking status. Methods for dealing with partial dates for prior and concomitant medications are described in Section 9.5.1. Methods for dealing with partial dates for start/end of AEs and missing relationship of AEs to study drug are described in Section 12.1. Otherwise, missing data will not be imputed.

Missing data due to Coronavirus Disease 2019 (COVID-19): In the unlikely event of site closure or restricted access due to COVID-19, where trial subjects are not able to come to the investigational site for protocol-specified visits, alternative methods for assessments (e.g., phone contact, virtual visit, alternative location for assessment (i.e., home health visits, including local labs) may be implemented when necessary and feasible, upon consultation with Sponsor. Shipment of investigational product to the subject's home may also be implemented, where permitted. Any missed visits or procedures due to COVID-19 will be captured on the appropriate electronic Case Report Form (eCRF), with the reason for missing data being attributed to COVID-19. All data collected in the eCRF concerning missing assessments will be reported in the listings.

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9. Demographic, Other Baseline Characteristics and Medication

9.1. Subject Disposition and Withdrawals

Subject disposition and withdrawals will be presented for the enrolled population by randomized treatment arm or screen failure, considering the following summaries:

- Number of subjects randomized.
- Number of subjects who discontinued treatment prior to completing the treatment period.
- Reason for treatment discontinuation.
- Number of subjects completing the study.
- Reason for early withdrawal.
- Number of subjects for whom the follow-up visit was performed.
- Number of subjects entering the VGN-TED-302 extension study.
- Number of subjects for whom the extended follow-up contact was successfully made.
- Number of subjects included/excluded in each analysis population, with reasons for exclusion summarised.

All data on subjects' disposition will be provided in listings for the enrolled population.

Subject level data on informed consent and unmet eligibility criteria will be listed for the enrolled population.

Subject level data for inclusion/exclusion in analysis populations will also be listed for the enrolled population.

9.2. Protocol Deviations

All data available for protocol deviations will be listed.

9.3. Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized for the ITT, safety and PP populations. The following variables will be summarized:

- Age (years)
- Sex
- Childbearing potential (female only)
- Race
- Ethnicity
- Smoking status
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Heart rate (HR) (beats/min)
- Respiratory rate (breaths/min)
- Temperature (°C)

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Height may be reported in cm or inches. For the summaries, inch values will be converted to cm using the following formula:

$$Height\ (in\ cm) = Height\ (in\ inches) \times 2.54$$

Weight may be reported in kg or lbs. For the summaries, lbs. values will be converted to kg using the following formula:

$$Weight\ (in\ kg) = Weight\ (in\ lbs) \times 0.45359237$$

Temperature may be reported in °C or °F. For the summaries, °F values will be converted to °C using the following formula:

$$Temperature\ (in\ ℃) = \left(Temperature\ (in\ ℉) - 32\right) \times \frac{5}{9}$$

All data on demographics and Baseline characteristics will be presented in a by-subject listing for the ITT population. Data will be presented in the converted units.

9.4. Medical History and Concomitant Diseases

A complete medical history, including past surgeries will be obtained at the screening visit. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or later.

Medical history will be summarized for the ITT population and will consist of counts and percentages by system organ class (SOC) and preferred term (PT). Summaries will be sorted by descending percentage in SOC, then by PT within SOC for the total group.

Subjects will be counted only once for each SOC or PT in the event that they have multiple records of the same SOC or PT.

All medical history data will be listed for the ITT population.

9.5. Medication

9.5.1. Prior and Concomitant Medications

Prior and concomitant medications should be reviewed at Screening and updated throughout the study. Any treatments given during the study other than linsitinib, including blood transfusions, parenteral fluids, over-the-counter medications, and herbal preparations, are considered to be concomitant therapies and must be recorded on the eCRF. Medications will be collected up to 6 months prior to dosing.

All medications will be coded using the World Health Organization (WHO) Drug coding dictionary version Sep 2021 or later.

Prior medications are defined as medications that stopped before the first dose of study drug. Concomitant medications are defined as medication which are ongoing or starting on or after the date of the first dose of study drug and prior to or on the date of the last dose of study drug.

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In the presence of partial dates, medications will be considered concomitant unless it is clear from the end date of the medication that it is not. The following approach will be taken:

- If end day is missing, a medication will be considered concomitant unless end month/year is prior to month/year of first dose of study drug, regardless of completion of start date.
- If end day/month is missing, a medication will be considered concomitant unless and year is prior to year of first dose of study drug, regardless of completion of start date.
- If end day/month/year is missing, a medication will be considered concomitant, regardless of completion of start date.

All medications which are not classed as concomitant, will be classed as prior.

Prior and concomitant medications will be summarised by preferred name and Anatomical Therapeutic Chemical (ATC) level 2, for the ITT population. Subjects will only be counted once per medication. All data on prior and concomitant medications will be listed for the ITT population.

9.5.2. Other Therapies

Data on surgeries after the start of the study will be listed for the ITT population.

9.6. Extent of Exposure and Treatment Compliance

Subjects will be dosed in the clinic on Day 1 and Weeks 3, 6, 15 and 24. Otherwise, subjects will be responsible for their own dosing. As such data on extent of exposure and compliance will generally consist of dispensation, return and loss (number of tablets) of study drug.

Extent of exposure and compliance will be summarized for the ITT, Safety and PP populations.

Summaries of extent of exposure and compliance will consider the following:

- Number of subjects with study drug administered and dispensed
- Treatment duration (days)
- Total dose (mg), split by Placebo and linsitinib
- Compliance (%)

Treatment duration, total dose and compliance will be summarized as continuous variables.

Treatment duration will be calculated as follows:

$$Treatment\ duration = Date\ of\ last\ dose - date\ of\ first\ dose + 1$$

Total dose will be calculated as follows:

$$Total\ dose\ (mg) = (Total\ tablets\ dispensed - total\ tablets\ returned)\ x\ 75$$

Compliance with study drug will be calculated as follows:

$$Compliance\ (\%) = \frac{Total\ tablets\ dispensed - total\ tablets\ returned}{Total\ tablets\ expected\ to\ have\ been\ taken}$$

where the total tablets expected to have been taken is calculated by the duration of treatment in days, multiplied by four (as subjects are scheduled to take two tablets twice daily).

All data collected on study drug administration and dispensation will be listed. Individual subject data on study drug compliance will also be listed.

10. Efficacy

The Hochberg procedure[1] will allow for multiple tests of the primary and secondary efficacy estimands for the pairwise comparisons of each active treatment (75 mg Linsitinib or 150 mg Linsitinib) versus placebo.

For the primary endpoint main estimand, the following hypothesis tests will be considered:

$H_0(1)$: Proportion of Responders Placebo ≥ Proportion of Responders Linsitinib 75 mg vs.

$H_A(1)$: Proportion of Responders Placebo < Proportion of Responders Linsitinib 75mg

$H_0(2)$: Proportion of Responders Placebo ≥ Proportion of Responders Linsitinib 150 mg vs.

$H_A(2)$: Proportion of Responders Placebo < Proportion of Responders Linsitinib 150mg

Both 75 mg and 150 mg active doses will be tested versus placebo. The p-values from both comparisons will be ordered by magnitude If the one-sided p-value for both tests are <0.025, then $H_0(1)$ and $H_0(2)$ will both be rejected, confirming a significant difference between both linsitinib doses and placebo.

If the larger of the two one-sided p-values is >0.025, then the smaller value will be compared to alpha = 0.0125. For example, if the one-sided p-value for the comparison of the 75 mg dose to placebo was p=0.03, then $H_0(1)$ would not be rejected. If the one-sided p-value for the comparison of the 150 mg dose to placebo was p=0.02 and is the smaller one, then $H_0(2)$ would not be rejected, but it would be rejected for p=0.01, for example.

If both one-sided p-values are >0.025 then neither $H_0(1)$ nor $H_0(2)$ would be rejected.

Secondary endpoints will be tested in a hierarchical manner in the order specified in Section 5.2, if the primary hypothesis is met. If both the 75 mg and 150 mg doses are found to significantly outperform placebo for the primary efficacy endpoint, then the Hochberg procedure will be used to test the 75 mg and 150 mg doses for secondary efficacy endpoint 1. If both the 75 mg and 150 mg doses are found to significantly outperform placebo for secondary efficacy endpoint 1, then the Hochberg procedure will be used to test the 75 mg and 150 mg doses for secondary efficacy endpoint 2 and so on. However, unless both doses are significant at the 0.025 level for a given estimand, then the hierarchical testing stops at this estimand. In the case that the p-value of the 'better dose' is <=0.0125, then this dose is considered as significant in a confirmatory way still for the given estimand. Otherwise, the confirmatory testing only includes the estimands prior to the given estimand.

Efficacy outputs are concerned with data from CSS, CAS, and GO-QoL. All data related to these assessments will be listed for the ITT population.

10.1. Primary Efficacy Estimands and Analysis

The analysis of the main estimand for the primary efficacy 'proptosis response' will be performed using Cochran-Mantel-Haenszel (CMH) test statistics by considering of the strata smoking status (smoker/non-smoker) at Baseline on the ITT population at a one-sided significance level alpha = 2.5%. Prior to application of CMH, missing values of proptosis measurement at Week 24 will be multiple imputed (See Section 7.1 for details). A table will be provided to detail the pattern of missing data. The common risk difference between the linsitinib treatment groups and placebo and the 95% confidence interval for the risk difference will be calculated, with associated p-value. The p-value will be based upon a transformed Wilson-

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Hilferty CMH test statistic.Example SAS code for the primary efficacy analysis is included in the Appendix. The code used in the analyses may be updated.

The analysis described above for the main estimand will be repeated on the PP population as supportive analysis.

A supportive complete case analysis will be provided for the ITT population where only complete data is used i.e., there is no multiple imputation, or carry forward of data to 24 weeks in the event of death.

A frequency table will be provided with number and percentage (with 95% confidence interval based on normal approximation) of subjects with proptosis response at each scheduled post-Baseline visit on the ITT and the PP populations. Descriptive results of the comparison between each linsitinib treatment group and placebo will consist of difference in proportion with 95% confidence interval (based on normal approximation) and will be provided for all visits on the ITT and PP populations. Testing here is exploratory only.

10.2. Secondary Efficacy Estimands and Analyses

10.2.1. Secondary Efficacy Endpoint 1 'Mean change from Baseline to Week 24 in proptosis measurement in the primary study eye':

The statistical analysis of the main and the second estimand of this secondary efficacy endpoint will be performed using an using a Mixed-effect Model Repeated Measures (MMRM) analysis with change from Baseline in proptosis measurement as dependent variable, and with treatment group, visit, the treatment-by-visit interaction, Baseline proptosis measure, the interaction between Baseline proptosis measure and visit, and Baseline smoking status (smoker/non-smoker) as independent covariates with fixed effect. The MMRM model will be applied after the construction of the estimands. Prior to application of MMRM, missing values of proptosis measurement up to Week 24 will be multiple imputed (See Section 7.1 for details). A table to detail the pattern of missing data will be provided as part of the analysis of the primary efficacy endpoint.

The Kenward–Roger method will be used to estimate the degrees of freedom, and unstructured covariance will be assumed. The mean difference between each linsitinib treatment group and placebo will be estimated on the treatment-by-visit interaction at the Week 24 visit, along with its 95% confidence interval, and the p-value for the one-sided test.

The least squared means from the MMRM will be plotted at each visit, with 95% confidence intervals.

Above-described analysis will be repeated on the PP population as supportive analysis.

A supportive complete case analysis will be provided for the ITT population where only complete data is used i.e., there is no multiple imputation, or carry forward of data to 24 weeks in the event of death. The least squares means from the MMRM will be plotted at each visit, with 95% confidence intervals.

A further supportive analysis will be provided for the ITT population where the analysis of the main estimand will be repeated but considering absolute value of proptosis (rather than change from baseline). The supportive complete case analysis will also be repeated considering absolute value of proptosis. Absolute value of proptosis will be the dependent variable and the covariates will be the same as those outlined in the change from baseline model. Similar plots of least squared means will be provided.

Summary tables of the actual values and changes from Baseline in proptosis for the primary and non-study eyes will be provided by treatment group for each scheduled visit. Descriptive comparison between each linsitinib treatment group and placebo will be provided for the visits of the treatment period (Week 3 to Week 21) except for Week 24, but also for all visits on the ITT and PP populations. Testing here is exploratory

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only. The mean (+/- standard deviation) of absolute value and change from baseline in proptosis will be plotted over time for the primary and non-study eyes for the ITT and PP populations.

10.2.2. Secondary Efficacy Endpoint 2 'Overall responder rate (percentage of subjects with ≥ 2-point reduction in CAS and ≥ 2mm reduction in proptosis from Baseline in the primary study eye, provided there is no corresponding deterioration (≥2-point/ mm increase) in CAS or proptosis in the contralateral non-study eye at Week 24'

A similar analysis approach as described in Section 10.1 for the primary efficacy estimand will be applied for this secondary efficacy estimand.

10.2.3. Secondary Efficacy Endpoint 3 'Percentage of subjects with a CAS value of 0 or 1 at Week 24 in the primary study eye'

A similar analysis approach as described in Section 10.1 for the primary efficacy estimand will be applied for this secondary efficacy estimand. Note that a table to detail the pattern of missing data will be provided as part of the analysis of the second secondary efficacy endpoint.

10.2.4. Secondary Efficacy Endpoint 4 'Mean change from Baseline to Week 24 in the GO-QoL questionnaire overall score'

The analysis of the estimand of this secondary efficacy endpoint will be performed in a similar manner to the analysis of the secondary efficacy endpoint 1 'Mean change from Baseline to Week 24 in proptosis measurement in the primary study eye', described in Section 10.2.1.

10.3. Exploratory Efficacy Endpoints

10.3.1. Exploratory Efficacy Endpoint 1 'CSS individual responses for each component of clinical severity from Baseline to Week 24'

A summary table of CSS individual items by visit will be provided. A frequency table with number and percentage of subjects with response at each scheduled post-Baseline visit until Week 24 (based on pre-defined minimum change from Baseline, see Table 2) will be presented for each CSS item by treatment group. The comparison between each linsitinib treatment group and placebo with regards to each CSS item at Week 24 will be performed using CMH test statistics by considering of the strata smoking status (smoker/non-smoker) at Baseline on the ITT population at a one-sided significance level alpha =2.5%. Analyses will be repeated for the primary study eye and the non-study eye.

Table 2: Response Criteria for Individual CSS Components

CSS Item	Severity Assessment	Response Criteria
Lip aperture	Distance between lid margins (mm)	Decrease ≥ 2mm
Swelling of the eyelids	Absent, mild, moderate, severe	Decrease ≥ 1 grade
Redness of the eyelids	Absent, present	Decrease ≥ 1 grade
Redness of the conjunctiva	Absent, present	Decrease ≥ 1 grade
Conjunctival edema	Absent, present	Decrease ≥ 1 grade
Inflammation of the caruncle of plica	Absent, present	Decrease ≥ 1 grade
Subjective diplopia score	0 – 3 scale	Decrease ≥ 1 grade
Corneal involvement	Absent, punctate keratopathy, ulcer	Decrease ≥ 1 grade
Eye muscle involvement	Ductions in degrees	Increase ≥8° in at least one direction of gaze
Optic nerve involvement – best corrected visual acuity	Snellen chart	Change of best corrected visual acuity by ≥ 2 lines on Snellen chart

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Color vision	Normal, abnormal non-significant change, abnormal significant change	Abnormal significant change
Optic disc	Normal, abnormal non-significant change, abnormal significant change	Abnormal significant change
Relative afferent pupillary defect	Absent, present	Decrease ≥ 1 grade
Visual fields (if optic nerve compression is suspected)	Normal, abnormal non-significant change, abnormal significant change	Abnormal significant chance

10.3.2. Exploratory Endpoint 2 'Mean change from Baseline to Week 24 in the CAS'.

A frequency table of number and percentage of subjects with presence/absence of each of the 7 items of CAS (see Table 3) will be presented for each scheduled visit by treatment group. The overall CAS score is ranging from 0 (all 7 items are absent) to 7 (all 7 items are present). A summary table of the overall CAS score will be provided for actual values and change from Baseline for each scheduled visit by treatment group. The comparison between each linsitinib treatment group and placebo in the CAS overall score at Week 24 will be performed using a MMRM analysis with change from Baseline in CAS score as the dependent variable, and with treatment group, visit, treatment-by-visit interaction, Baseline CAS score, Baseline CAS score-by-visit interaction, and Baseline smoking status (smoker/non-smoker) as independent covariates with fixed effect. The Kenward–Roger method will be used to estimate the degrees of freedom, and unstructured covariance will be assumed. The mean difference between each linsitinib treatment group and placebo will be estimated on the treatment-by-visit interaction at the Week 24 visit, along with its 95% confidence interval, and the p-value for the one-sided test. Analyses will be repeated for the primary study eye and the non-study eye.

Table 3: CAS

Description of Sign/Symptoms
1. Spontaneous retrobulbar pain.
2. Pain on attempted upward or downward gaze
3. Redness of eyelids
4. Redness of conjunctive (due to active TED/GO associated-inflammation)
5. Swelling of caruncle or plica
6. Swelling of eyelids (due to active TED/GO associated-inflammation)
7. Swelling of conjunctiva (chemosis)

Each item is scored (1=present; 0=absent) and summed for a total score out of 7.

10.3.3. Exploratory Endpoint 3 'Overall responder rate at Week 24 stratified by the level of response (high responders, responders, low responders, and non-responders).

To further explore the response based on both proptosis and CAS reduction, each subject will be classified into one of 4 response categories at Week 24:

[Proprietary responder-classification thresholds redacted - confidential]

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[Proprietary responder-classification thresholds redacted - confidential]

A frequency table with number and percentage of subjects with overall high response, overall response, overall low response and no response at Week 24 will be presented by treatment group. A logistic regression analysis will be used to compare the treatment groups on the basis of this ordered 4-category classification. Only treatment will be included as an independent variable. For the linsitinib treatment groups, the odds ratio vs. placebo (with 95% confidence interval) will be presented, with associated p-value.

10.3.4. Exploratory Endpoint 4 ‘Mean change from Baseline to Week 24 in the GO-QoL questionnaire visual functioning (VF) and appearance (A) subscale scores’.

A summary table of GO-QoL VF and A subscale scores will be provided for actual values and change from Baseline for each scheduled visit by treatment group. The comparison between each linsitinib treatment group and placebo in the GO-QoL VF and A subscale scores at Week 24 will be performed a MMRM analysis with change from Baseline in subscale score as the dependent variable, and with treatment group, visit, treatment-by-visit interaction, Baseline subscale score, Baseline subscale score-by-visit interaction, and Baseline smoking status (smoker/non-smoker) as independent covariates with fixed effect. The Kenward–Roger method will be used to estimate the degrees of freedom, and unstructured covariance will be assumed. The mean difference between each linsitinib treatment group and placebo will be estimated on the treatment-by-visit interaction at the Week 24 visit, along with its 95% confidence interval, and the p-value for the one-sided test.

10.3.5. Exploratory Endpoint 6 ‘Mean change from Baseline to Week 24 on the motility component of the CSS’.

Motility in vertical and horizontal gaze is evaluated during the CSS assessment. Motility will be graded from 0° to 45° in four directions. The subject will be asked to look as far as possible up (supraduction), down (infraduction), right (abduction), and left (adduction) while the observer points a bright light at the eyes and studies the light reflex on the surface of the eye. If the light reflex hits the edge of the pupil, the eye has rotated 15o; if the light reflex hits between the pupil edge and the limbus, the eye has rotated 30°; if the light reflex hits the limbus, the eye has rotated 45°. The four values (in degrees) for the primary study eye are summed for each subject.

A summary table with actual values and change from Baseline will be presented for the motility component of the CSS by treatment group for each scheduled visit. The comparison between each linsitinib treatment group and placebo at Week 24 will be performed using a MMRM analysis with change from Baseline in motility as the dependent variable, and with treatment group, visit, treatment-by-visit interaction, Baseline motility, Baseline motility-by-visit interaction, and Baseline smoking status (smoker/non-smoker) as independent covariates with fixed effect. The Kenward–Roger method will be used to estimate the degrees of freedom, and unstructured covariance will be assumed. The mean difference between each linsitinib treatment group and placebo will be estimated on the treatment-by-visit interaction at the Week 24 visit, along with its 95% confidence interval, and the p-value for the one-sided test. Analyses will be repeated for the primary study eye and the non-study eye.

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10.3.6. Exploratory Endpoint 7 'Diplopia responder rate'

A frequency table with the subject diplopia score at each visit will be provided for the primary study eye and non-study eye.

Diplopia response is defined as subjects with Baseline diplopia > 0 in primary study eye who have a reduction of ≥ 1 grade with no corresponding deterioration (≥1 grade worsening) in the contralateral non-study eye at Week 24. For the subgroup of subjects with Baseline diplopia > 0 the number and percentage of subjects with diplopia response at each scheduled post-Baseline visit until Week 24 will be summarised. The comparison between each linsitinib treatment group and placebo at Week 24 will be performed using CMH test statistics by considering of the strata smoking status (smoker/non-smoker) at Baseline on the ITT population at a one-sided significance level alpha =2.5%.

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11. Pharmacokinetics

The PK analyses will be conducted for linsitinib, and will include a listing and summary of concentrations, derived PK parameters and graphic presentation of data as described below. The non-compartmental analysis (NCA) will be performed using appropriate software, e.g., Phoenix™ WinNonlin® (Version 8.0 or higher, Certara Corporation) and/or SAS® (Version 9.4 or higher, SAS Institute Inc.).

Plasma samples will be analyzed for linsitinib using validated assays. PK parameters will be derived for linsitinib according to the methods described in SAP Section 11.4.

11.1. PK Sampling Schedule

Blood samples for determination of the plasma concentration of linsitinib are collected at the time points specified in the Schedules of Activities (see Table 4). The focused schedule for PK blood sampling times is outlined in Table 4 (with collection windows of +/- 5 minutes, all completed at the study clinic).

Table 4: PK Blood Sampling Times

Visit	Timing
Day 1	pre-dose of study drug and hours 2, 3, and 4 post-dose
Week 3	pre-dose of study drug and hours 2, 3, and 4 post-dose
Week 6	pre-dose of study drug
Week 6	2 hours post dose*
Week 15	pre-dose of study drug
Week 24	**

*Approximately one to two subjects at each site will have an additional PK sample collected at 2 hours post-dose at Week 6.
**Last dose of study medication is taken the evening prior to the Week 24 visit.
Actual times of sampling and actual dosing times of linsitinib or matching placebo are recorded.

11.2. Plasma PK Endpoint

One of the exploratory objectives of this study is to: evaluate PK parameters of linsitinib to estimate exposure and understand PK-PD relationships.

A variety of PK parameters will be determined from the plasma concentrations of linsitinib (see Section 11.4).

11.3. Presentation of Concentration Data

11.3.1. Handling of Missing Data

No imputation of missing PK concentrations will be done.

11.3.2. Handling of the Difference between the Scheduled and the Actual Sampling Times.

The actual clock time for dosing and the actual clock time for each collection time for the PK samples will be recorded. For all sampling times, the actual sampling times will be calculated as the difference between the sample collection actual clock time and the actual clock time of dosing. The actual post-dose sampling times expressed in hours and rounded off to 3 decimal places will be used to calculate the PK parameters; pre-dose samples occurring prior to dosing will be reported as zero (0.000), regardless of the time difference.

Scheduled sampling times will be presented in concentration tables and mean graphs, while actual sampling times will be presented in the individual graphs. A by-subject listing of the actual times for PK

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collections will be provided for PK samples. If the actual sampling time is absent, then scheduled time will be used for tabulation, graphical representation and PK calculation purposes.

11.3.3. Listing and Presentation of Individual PK Data

The data will be handled as follows for the graphical presentation of individual plasma concentrations and for the derivation of the PK parameters (using actual sampling times):

- The time of collection of the pre-dose sample will be set to zero (time 0).
- Actual post-dose sampling times are expressed relative to the time of dosing (if the actual time of sampling is missing, the planned time will be used).
- Pre-dose plasma concentrations below the limit of quantification (BLQ) will be treated as zero;
- Concentration values BLQ prior to the first quantifiable concentration will be treated as zero.
- Post-dose BLQ values after the first quantifiable time point will be set to zero for calculation of plasma concentration summary statistics unless they are between two quantifiable values when they will be set to missing.
- Additionally, for calculation of PK parameters and individual profile plots, BLQ values after C_{max} will be set to missing.

Samples taken far outside the sampling windows may be excluded from by-time point summary statistics; this will be determined prior to unmasking by the Pharmacokineticist.

11.3.4. Summary of PK Concentrations

Listings and descriptive statistics (number of observations, number of observations BLQ, arithmetic mean, SD, arithmetic coefficient of variation (CV), median, minimum, and maximum) of the concentrations over time will be provided using the PK Population. The following rules will be applied while presenting summary statistics:

If more than half of the measured values are BLQ at any blood sampling time point for which the summary statistics are to be calculated, the statistics will not be tabulated for that time point, and will be shown as “N.C.” If a summary statistic cannot be calculated for a particular point, the summary statistic will be shown as “N.C.”

Plots for individual and mean plasma concentration versus time curves will be presented using linear and semi-log scales for linsitinib.

11.4. PK Parameters Derivation

Plasma samples from linsitinib will be used to calculate the PK parameters outlined below by standard non-compartmental methods. The PK Parameter Set will be used to calculate PK parameters.

The PK parameters (see Table 5) will be obtained by a Syneos Health PK scientist using WinNonlin with the following specifications:

1. Plasma model, dosing type: extravascular

2. Calculation of Area under the concentration-time curve (AUC): Linear up log down

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Table 5: PK Parameters

Parameter	Definition	Method of Determination
T_{lag}	Time prior to the first measurable (non-zero) concentration	Observed directly from data
T_{max}	Time of maximum observed concentration	Observed directly from data
C_{max}	Maximum observed concentration	Observed directly from data
C_{min}	Minimum observed concentration	Observed directly from data (Week 3 only)
$AUC_{0\text{-last}}$	AUC over the dosing interval from time 0 to the last measured concentration	Linear up log down
$AUC_{0\text{-}4}$	Area under concentration-time curve calculated from time zero to time 4h	Linear up log down
*$AUC_{0\text{-}\tau}$	Area under concentration-time curve for one dosing interval (τ) at steady-state	Linear up log down (Week 3 only)
C_{max}/D	Maximum observed concentration corrected for dose	C_{max}/Dose
$AUC_{0\text{-last}}$/D	AUC over the dosing interval from time 0 to the last measured concentration corrected for dose	$AUC_{0\text{-last}}$/D
$AUC_{0\text{-}4}$/D	Area under concentration-time curve calculated from time zero to time 4h corrected for dose	$AUC_{0\text{-}4}$/D
*$AUC_{0\text{-}\tau}$/D	Area under concentration-time curve for one dosing interval (τ) at steady-state corrected for dose	Linear up log down (Week 3 only)
*λ_z or K_{el}	Apparent first-order terminal elimination rate constant.	Estimated by linear regression of the terminal elimination phase of the log-linear drug concentration-time curve. Best fit method will be used to calculate the K_{el} from at least 3 post C_{max} concentration data points excluding the C_{max}. R_{sq} adjusted, the goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of K_{el} must be ≥ 0.8. The timepoint where ln-linear K_{el} calculation begins ($K_{el\ Lower}$) and the actual sampling time of the last measurable concentration used to estimate the K_{el} ($K_{el\ Upper}$), as well as the R_{sq} adjusted for the ln-linear regression for the calculation of the elimination rate constant will be listed. If the K_{el} cannot be measured (e.g.: fewer than 3 non-zero concentrations in the terminal elimination phase), then elimination related PK parameters (K_{el}, $K_{el\ Lower}$, $K_{el\ Upper}$, R_{sq} adjusted, $t_{1/2}$, and V_z/F) and CL_{ss}/F and $AUC_{0\text{-}\tau}$ will not be reported for PK profiles. If R_{sq} adjusted < 0.8, then K_{el}, and its related PK parameters (K_{el}, $K_{el\ Lower}$, $K_{el\ Upper}$, R_{sq} adjusted, $t_{1/2}$, and V_z/F) will be flagged in individual listings and excluded from summary statistics. (Week 3 only)
*$t_{1/2}$	Apparent terminal elimination half-life	Calculated as ln(2)/K_{el} (Week 3 only)
*CL_{ss}/F	Apparent total body clearance at steady-state	Calculated as Dose/$AUC_{0\text{-}\tau}$ (Week 3 only)
*V_z/F	Apparent Volume of distribution at steady-state	Calculated as Dose/(K_{el} × $AUC_{0\text{-}\tau}$) (Week 3 only)

*At Week 3, plasma concentrations are expected to have reached steady-state; therefore, the concentration at pre-dose will be duplicated and used as the derived 12-hour concentration to calculate the designated PK parameters.

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11.4.1. PK Parameters Summarization

PK parameters and concentrations data will be summarized using the descriptive statistics outlined in Table 6.

Table 6: Descriptive Statistics for PK Parameters

Variable	Summarized with:
PK concentration at each nominal time point	n, arithmetic mean, SD, arithmetic CV(%) (calculated as 100*SD/mean), median, minimum, and maximum
AUCs, C_{max}, $C_{min,}$ CL_{ss}/F and V_z/F	n, arithmetic mean, SD, arithmetic CV(%) (Calculated as 100*SD/mean), geometric mean, geometric CV(%) (calculated as $100*\sqrt{e^{z^2}-1}$, where z^2 is the variance of the log-transformed data), minimum, median and maximum
$t_{1/2}$, K_{el}	n, arithmetic mean, SD, arithmetic CV(%) (calculated as 100*SD/mean), median, minimum, and maximum
T_{max} and T_{lag}	n, minimum, median, and maximum

The following rule will be applied for presenting PK parameters summary: If the number of subjects for whom the PK parameters cannot be computed exceeds half the total, data will not be tabulated for that summary, and the result will be shown as “N.C.”

The degree of precision in reporting PK parameters will be as described in Table 7.

Table 7: PK Parameter Reporting Precision

Statistics	Degree of Precision
Minimum, Maximum	3 significant digits or as needed based on actual measured values (for example PK concentrations)
Mean (arithmetic and geometric), Median	4 significant digits or as needed based on actual measured values (for example PK concentrations)
Standard deviation	5 significant digits or as needed based on actual measured values (for example PK concentrations)
CV% and Geometric CV%	1 decimal point or as needed based on actual measured values (for example PK concentrations)

For PK concentration and parameter listings, the final reportable results or data will be presented by rounding off to 2 decimal digits, except for the following situations (this applies to individual data):

- Kel data, and Rsq adjusted: rounded off to four decimal digits.
- PK parameters related to time such as T_{max}, T_{lag}, $K_{el\ Lower}$, and $K_{el\ Upper}$ must be reported with the same precision as the actual sampling time: rounded off to 3 decimal digits.
- Concentration versus time data: reported as they appear in corresponding dataset.

11.5. Planned Statistical Models for PK Parameters and Concentrations

No formal statistical models for PK analysis are planned.

11.6. Interim Analyses

No formal interim PK analysis is planned.

11.7. Deviation from Analyses Planned in Protocol.

Not applicable.

12. Safety

The population used for safety analyses will be the Safety Population. Safety will be assessed based on AEs, clinical laboratory data, vital signs, ECG parameters, physical examinations, pretibial myxedema examination and ophthalmic examination.

12.1. Adverse Events

AEs will be collected from the time the subject signs the informed consent form through the follow-up period. AEs will include changes in subject's condition. AEs will be coded using the MedDRA coding system (version 24.1 or later) and summarized by SOC and PT.

AEs will be defined as TEAEs if they begin or worsen after the first dose of study drug. Events which start more than 14 days after the last dose of study drug will not be defined as treatment-emergent. Events with incomplete start dates will be considered treatment-emergent if:

- Day is missing and the year is after the year of the first dose of study drug.
- Day is missing and the year is equal to the year of the first dose of study drug and the month is equal to or after the month of the first dose of study drug.
- Day and month are missing, and the year is equal to or after the year of the first dose of study drug.
- Year is missing.
- Start date is completely missing.

However, events where the end date of the AE is prior to the first dose if study drug will not be considered treatment-emergent, regardless of missing data in the start date.

In line with the above approach, AEs with incomplete start dates will be considered treatment-emergent unless there is a clear indication that the event was not treatment-emergent.

Only treatment-emergent events will be included in the summary tables. All information on all AEs (treatment-emergent or otherwise) will be listed.

AEs will be categorized in terms of its potential relationship to the study drug as unrelated, unlikely related, possibly related, probably related or definitely related. For the purposes of reporting, AEs which are unrelated or unlikely related will be considered as **Not Related**. AEs which are possibly related, probably related or definitely related will be considered as **Related**. AEs with missing relationship will be considered as **Related**.

An overall AE incidence summary table will be produced and will include the number and percentage of subjects with the follow:

- At least one TEAE
- At least one ocular TEAE
- At least one severe TEAE
- At least one related TEAE
- At least one TEAE leading to withdrawal
- At least one serious TEAE
    - Resulting in death
    - Is life-threatening
    - Requires or prolongs in-patient hospitalization
    - Results in persistent of significant disability or incapacity
    - Congenital anomaly or birth defect

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- Other significant medical event

For event types included in the overall AE incidence summary table, tables summarizing events by SOC and PT will be produced, sorting by decreasing frequency of SOC then PT within SOC in the total group. If a subject has multiple events for the same SOC or PT, then they are counted only once in that SOC or PT.

TEAEs will also be summarised by SOC, PT and maximum severity. Subjects who experienced the same coded event more than once are counted only once for the coded event with the highest grade.

All AEs will be included in a by-subject listing. Specific subject listings will be included considering deaths, serious TEAEs and TEAEs leading to withdrawal.

12.2. Laboratory Evaluations

Testing of clinical laboratory samples will be carried out by the central clinical laboratory using validated methods and will include the tests listed in Table 8.

All summaries of laboratory data will be based upon results in Standard International (SI) units. Laboratory values will be summarised at each visit, with change from Baseline.

The laboratory parameters collected in this study are listed in Table 8.

All laboratory data, including results in the original units, will be listed.

Pregnancy test data will be listed only.

Table 8: Laboratory Parameters

Category	Parameter
Hematology	Hematocrit
	Hemoglobin
	Platelet count
	Red blood cell count
	White blood cell count with differential
	HbA1c glucose
Chemistry	Albumin
	Alkaline phosphatase
	ALT; serum glutamic pyruvate transaminase (ALT; SGPT)
	AST; serum glutamic oxaloacetic transaminase (AST; SGOT)
	Blood urea nitrogen
	Calcium
	Creatinine
	Glucose
	Total bilirubin
	Total protein
	Magnesium
	Sodium
	Potassium
	Chloride
	Bicarbonate
	LDH
	Gamma-glutamyl Transferase (GGT)
	Lipase
	Total cholesterol
	Triglycerides
	HDL
	LDL

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	INR
	PT
	PTT
	Cotinine (urine)
Metabolic-Thyroid Function	FT4
	FT3
	Thyroid stimulating hormone (TSH)
Urinalysis	Appearance
	Bilirubin
	Color
	Glucose
	Ketones
	Leukocyte esterase
	Nitrite
	Occult blood
	pH
	Protein
	Specific gravity
	Urobilinogen
	Microscopic examination will be performed if leukocyte esterase, nitrite, and/or occult blood are positive (listed only)
Viral screen*	Hepatitis B surface antigen (HBsAg)
	Hepatitis C virus (HCV)
	HIV

* Viral screen is collected at Screening (or at unscheduled visits) only. Therefore, summaries concerning changes from baseline are not applicable.

12.3. Vital Signs

Vital signs (temperature, SBP and DBP, HR, and respiratory rate) and weight/BMI will be measured at Screening, the Baseline visit and during all Double-masked Treatment Period visits, Follow-up Period visits, and End of Study visit. Height will be measured only at Screening.

The actual value and change from Baseline to each visit will be descriptively summarised. A plot of vital signs parameters SBP, DBP and HR over time will be provided. This will consist of a box plot at each time point. Plots will be split by treatment group.

Temperature may be reported in °C or °F, height in cm or inches and weight in k or lbs. °F will be converted to °C, inches will be converted to cm and lbs. will be converted to kg for the summary tables using formulae as outlined in Section 9.3.

All vital sign data will be listed. Listings will use the converted units for temperature, height and weight.

12.4. ECG

All subjects will have 12-lead ECGs performed (in triplicate) at Screening, on the first day of dosing (Baseline/Day 1, pre-dose, hours 2, 3, and 4 post-dose) and during the Treatment Period at Week 3 (pre-dose, hours 2, 3, and 4 post-dose). The subsequent visits at 3-week intervals will require one triplicate ECG (starting at Week 6 visit); Weeks 6, 9, 12, 15, 18, 21 and 24, and Follow-up Period Weeks 28, 36, 48, 60, and 72. All ECGs should be recorded digitally and in triplicate (repeated 3 times at least 1 minute apart).

The actual value and change from Baseline at each visit/timepoint will be descriptively summarised for the following ECG parameters:

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- Mean Heart Rate (beats/min)
- QRS Duration (msec)
- QT Interval (msec)
- QTcB Interval (msec)
- QTcF Interval (msec)
- RR Interval (msec)
- PR Interval (msec)

Summary tables will consider the mean of the triplicate values. In the event that triplicate values are not available, the mean will be taken of the available records.

A plot of the ECG parameters listed above over time will be provided. This will consist of a box plot at each time point. Plots will be split by treatment group.

A categorical analysis of QTcF interval correction will also be presented, based on the number and percentage of subjects meeting or exceeding specific thresholds for QTcF interval and change from Baseline in QTcF interval. For change from Baseline, the mean of the triplicate measurements will be calculated at each visit/timepoint then the change from Baseline will be calculated. The number and percentage of subjects within the following thresholds will be summarized at each visit:

- >450 msec
- >470 msec
- >500 msec
- Increased from Baseline >60 msec and > 470 msec

ECG summaries will be provided by sex and overall. All ECG data will be included in a by-subject listing, including overall interpretation, findings and technical quality.

12.5. Physical Examination

A complete physical examination will be performed at Screening, Baseline and during the Double-masked Treatment Period on Weeks 6, 12, 18, and 24, and Follow-up Period Weeks 48 and 72. During the Double-masked Treatment Period, targeted physical examinations may be performed at any additional time at the discretion of the Investigator, based on AEs and positives from review of systems.

The following systems will be examined for a complete physical examination: HEENT, respiratory, cardiovascular, gastrointestinal, hepatobiliary, musculoskeletal, neurological, dermatological, and any areas pertinent to any AEs and positives from review of systems.

The proportion of examinations falling into the following categories will be summarized at each visit:

- Normal
- Abnormal Not Clinically Significant
- Abnormal Clinically Significant

All data on physical examinations will be included in a by-subject listing.

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12.6. Biomarkers (Exploratory Endpoint 5)

Blood samples will be analyzed for certain named biomarkers to provide information relevant to the PD properties of linsitinib. These biomarkers will include assessments of serum IGF-1at pre-dose on Day 1 and pre-dose on Weeks, 3 and 15 and at week 24. IGF-1R and phospho-IGF-1R assessments will be at pre-dose on Day 1 and 4 hours post-dose, and pre-dose on Weeks, 3 and 15 and at week 24. Additional blood samples will be collected for the purpose of exploratory biomarker assessments, which may include antibodies to IGF-1R, TSHR, thyroperoxidase (TPO), and thyroglobulin (Tg), as well as cytokines such as IL-6, IL-16, and RANTES. Collection of blood samples for these exploratory biomarkers will occur at pre-dose on Day 1, and pre-dose on Weeks 3 and 15, and at weeks 24 and 36.

A summary table of blood and serum biomarkers will be provided for actual values and change from Baseline for each scheduled visit by treatment group. The comparison between each linsitinib treatment group and placebo in blood and serum biomarkers at Week 24 will be performed using a MMRM analysis with change from Baseline in biomarker assessment as the dependent variable, and with treatment group, visit, treatment-by-visit interaction, Baseline biomarker assessment, Baseline biomarker assessment-by-visit interaction, and Baseline smoking status (smoker/non-smoker) as independent covariates with fixed effect. The Kenward–Roger method will be used to estimate the degrees of freedom, and unstructured covariance will be assumed. The mean difference between each linsitinib treatment group and placebo will be estimated on the treatment-by-visit interaction at the Week 24 visit, along with its 95% confidence interval, and the p-value for the one-sided test.

All data on Biomarkers will be listed.

12.7. Other Safety

All data on pretibial myxedema examination and ophthalmic examination will be listed.

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13. Interim Analyses

There is no planned interim analysis for this study.

14. Changes from Analysis Planned in Protocol

The Hochberg procedure for confirmatory testing of the primary and secondary estimands outlined in Section 10 has been updated.

For the analysis of Exploratory Endpoint 3 (Section 10.3.3), the ‘Non-Responders’ group has been updated to not include subjects with missing data.

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15. Programming Considerations

15.1. General Considerations

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow International Council for Harmonization (ICH) E3 guidance.

15.2. Table, Figure, and Listing Format

15.2.1. General

- All TFLs will be produced in landscape format unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

15.2.2. Headers

- All output will have the following header

```
Sling Therapeutics, Inc.
Confidential
Protocol: VGN-TED-301 (Syneos Health No. [Redacted]                    Page x of y
```

- TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table)
- The date the output was generated will appear along with the program name as a footer on each page

```
Data Version: DDMONYYYY                                    Program Name: xxx.SAS
Version and Execution Date: XXXX DDMONYYYY
```

15.2.3. Display Titles

- Each TFL will be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but Sponsor preferences are obtained before final determination. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title will be centered. The analysis set will be identified on the line immediately following the title and will be

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enclosed in parenthesis. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be one blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Population)

15.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column is on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include 'unit' in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

15.2.5. Body of the Data Display

15.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

15.2.5.2. *Table Conventions*

- Units will be included where available.
- For categorical parameters, all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

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- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, SBP will be presented as follows:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values will be output in the format: '0.xxx', where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999.
- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Values that round down to 0.0 will be displayed as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places.
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of AE data will be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by PT), drugs (by ATC1 code), and AEs (by PT) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated will be reported as '-'.
- The percentage of subjects will normally be calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Details will be described in footnotes or programming notes, as necessary.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote or programming note will be added describing whether the subject is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria.
- Where a category with a subheading (such as SOC) has to be split over more than one page, output the subheading followed by '(cont.)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

15.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

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- Missing data will be represented on subject listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate.
- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000). Missing portions of dates will be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject will be output as 'N/A', unless otherwise specified.
- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

15.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

15.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display
- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the TFL. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').
- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when multiple cross-references are displayed Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1.

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16. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs Standard Operating Procedure (SOP) [Redacted]

Syneos Health Developing Statistical Programs SOP [Redacted] Conducting the Transfer of Biostatistical Deliverables SOP [Redacted] and the SAS Programming and Validation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

17. References

1. Hochberg, Y. (1988). A Sharper Bonferroni Procedure for Multiple Tests of Significance. Biometrika, 75(4), 800–802.

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18. Appendix

[Proprietary statistical programming code redacted - confidential commercial information]

This document is confidential.

[Proprietary statistical programming code redacted - confidential commercial information]

This document is confidential.

[Proprietary statistical programming code redacted - confidential commercial information]

This document is confidential.