Sling Therapeutics

SLING THERAPEUTICS, INC.

CLINICAL STUDY PROTOCOL

STUDY NUMBER: VGN-TED-301

A Phase 2b, Randomized, Double-Mask, Placebo-Controlled, Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Linsitinib in Subjects with Active, Moderate to Severe Thyroid Eye Disease (TED)

Study Phase: 2b

Product Name: Linsitinib

IND Number: 157686

EudraCT Number: 2021-005000-36

NCT number: NCT05276063

Indication: Thyroid Eye Disease (TED)

Sponsor: Sling Therapeutics, Inc.

Sponsor Contact: PPD **, MD, FACG, FACP**

EU Consolidated Amendment 4: Version 6.4 –March 13, 2024

Italy: Original Protocol: Version 3.0 - November 12, 2021

Amendment 1: Version 3.4 - Italy July 11, 2022

Amendment 2: Version 4.4 – Italy January 17, 2023

Amendment 3: Version 5.4 – Italy September 19, 2023

Spain: Original Protocol: Version 3.0 - November 12, 2021

Amendment 1: Version 3.3 – Spain May 19, 2022

Amendment 2: Version 4.3 – Spain October 6, 2022

Amendment 3: Version 5.3 – Spain September 19, 2023

Revision History

The final approved Italy VGN-TED-301 v5.4 is the new VGN-TED-301 Consolidated v6.4 protocol. Changes noted in the table below only apply to Spain.

Edits to Table of Contents, spacing, formatting, typos, capitalizations, etc., that do not affect protocol content were corrected and are not included in the following tables.

Section/ Appendix	Revision Description
Changes to Spain 5.3 Protocol	Changes dated 13 March 2024
Title	A Phase 2b, Randomized, Double-Mask Placebo-Controlled, Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Linsitinib in Subjects with Active, Moderate to Severe Thyroid Eye Disease (TED)
Exclusion Criteria #17 and Section 1.3 Clinical Safety Data	Added additional potential risk TdP factors, e.g., hypokalemia and family history of Congenital Long QT syndrome
Section 4.2 Subject Withdrawal Criteria, #5 and Section 5.7 Study Medication and Management for Toxicity	Added the reintroduction of the study drug should not be allowed in case of toxicity of Grade ≥ 4.

Confidentiality Statement

This confidential document is the property of Sling Therapeutics, Inc., and it is provided for the use of the Investigator and other designated personnel solely in connection with the conduct of the study described herein. No information contained herein may be disclosed, except as necessary to obtain consent from persons who are considering participation in the study, without prior written approval of Sling Therapeutics, Inc.

INVESTIGATOR'S AGREEMENT

Study Title: A Phase 2b, Randomized, Double-Mask Placebo-Controlled, Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Linsitinib in Subjects with Active, Moderate to Severe Thyroid Eye Disease (TED)

This protocol is provided for use by you, your staff and the Institutional Review Board or Ethics Committee. The information contained in this document is confidential and belongs to Sling Therapeutics, Inc. Except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and not to disclose it to others (except where required by applicable law) nor use it for unauthorized purposes. In the event of actual or suspected breach of this obligation, Sling Therapeutics, Inc. must be promptly notified.

STUDY INVESTIGATOR SIGNATURE

By my signature below, I agree to conduct this clinical study in accordance with applicable government regulations or laws, and institutional/ethical review and informed consent practices. I have read the Investigator's Brochure and protocol. I agree to ensure the confidentiality of my subjects; however, I agree to make available to Sling Therapeutics, Inc. or designee the subject's medical chart specifically for the purposes of this clinical study. I am fully conversant with Good Clinical Practices (GCP) and agree to conduct the clinical study in accordance with these principles and the procedures described in this protocol. I am aware of my responsibilities as an Investigator.

Name: _____

Please print

Title: _____

Signature: _____

Date: _____

Address: _____

_____

_____

SPONSOR SIGNATURE

Study Title: A Phase 2b, Randomized, Double-Mask, Placebo-Controlled, Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Linsitinib in Subjects with Active, Moderate to Severe Thyroid Eye Disease (TED)

SPONSOR SIGNATURE

I have read and approve the protocol and appendices. My signature, in conjunction with the signature of the Investigator, confirms the agreement of both parties that the clinical trial will be conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to, the International Council for Harmonisation (ICH) Guidelines for GCP, the US Code of Federal Regulations and the ethical principles that have their origins in the Declaration of Helsinki, as well as all applicable privacy laws.

Name: CCI MD, FACG, FACP

Title: Chief Medical Officer

Signature: _____

Date: _____

Address: CCI

_____

SYNOPSIS

Name of Sponsor/Company: Sling Therapeutics, Inc.	
Name of Investigational Product: Linsitinib	
Title of Study: A phase 2b, randomized, double-mask, placebo-controlled, study to evaluate the safety, pharmacokinetics and efficacy of linsitinib in subjects with active, moderate to severe thyroid eye disease (TED)	
Study Center(s): Up to 40 study centers in the US, UK, Canada, Italy, Spain	
Studied Period: Actual date first subject screened: August-2022 Actual date first subject dosed: October-2022 Estimated date last subject completed: February 2025	**Phase of Development:** 2b

Objectives of the Study:

Primary Objective:

The primary objective is to study the 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.

Secondary Objectives (analyzed hierarchically):

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 Scale (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. 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.

Exploratory Objectives:

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Safety Objective:

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

Methodology/Study Design:

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 of which 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 have the option to enroll in the VGN-TED-302 Extension Study if they meet all criteria. 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 Extension Study if they meet all criteria (Section 2.3).

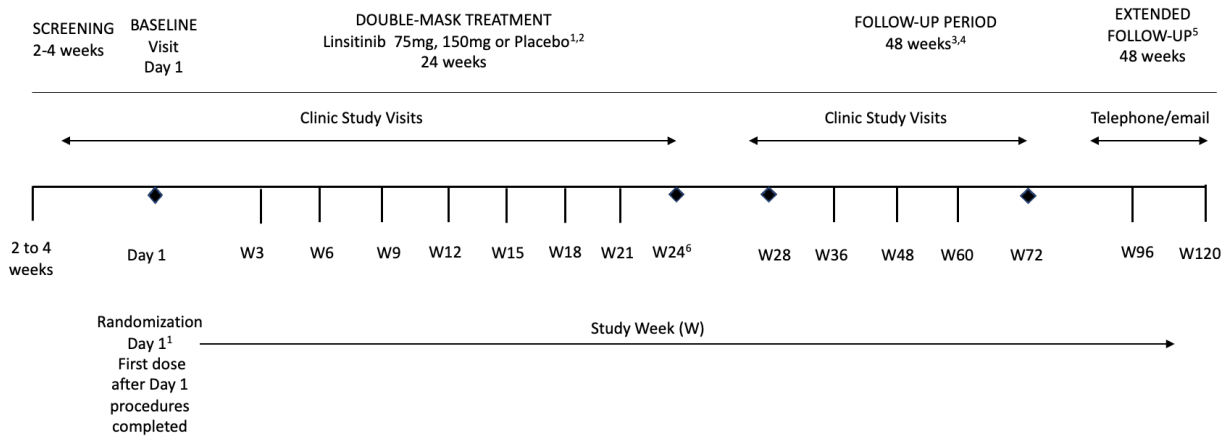
Subjects who prematurely discontinue study drug dosing at any time prior to completion of the 24-week clinic visit will return to the clinic and undergo the scheduled Week 24 assessments and will be encouraged to participate in the Follow-up Period unless they initiated another intervention due to lack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

Subjects who enter the Follow-up Period but prematurely discontinue the 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 the Schedule of Activities (Table 1).

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.

Number of Subjects (planned):

Approximately 75 men and women, ≥ 18 years of age with active, moderate to severe TED will be enrolled.

Diagnosis and Main Criteria for Inclusion in the Study:

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 participant's 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 not have 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 study drug. It is recommended that hormonal (ie: 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 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 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.

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 <1 g methylprednisolone or equivalent for the treatment of TED 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 steroids 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 Medical 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 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) and TdP risk factors, e.g., hypokalemia and family history of Congenital Long QT syndrome.
18. Use of drugs potentially associated with 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. (Section 12.2)
19. *Removed due to amendment.*
20. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN) according to age at Screening.
21. Serum creatinine > 2 x ULN for the reference range laboratory according to age at Screening.
22. 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.
23. Pregnant or lactating women.
24. 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.
25. 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.
26. Uncontrolled Human immunodeficiency virus (HIV), as judged by the Investigator, or positive hepatitis C, or hepatitis B.

Investigational Product, Dosage and Mode of Administration:

The investigational product is a white round shaped, biconvex, film coated tablet, for oral administration twice daily. Tablets will be in 75 mg strength or placebo. The planned treatments are 75 mg BID linsitinib, 150 mg BID linsitinib, and placebo BID. Doses are assigned randomly 1:1:1 to linsitinib or matching placebo (75 mg BID linsitinib:150 mg BID linsitinib: placebo BID).

Duration of Treatment:

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, as well as during clinic visits at Weeks 3, 6, and 15 (due to required CCI).

Dosing is required in the morning and in the evening, with approximately 12 hours between doses, and should be accompanied by a meal and approximately 240 mL of water. The duration of the study will be approximately 120 weeks per subject, depending on the duration of screening.

For additional instructions, please refer to the Pharmacy Manual.

Criteria for Evaluation:

The primary study eye will be defined as the more severely affected eye at the Baseline (Day 1) Visit. 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. If both eyes meet eligibility requirements but CAS versus proptosis are each more significant in opposite eyes the eye exhibiting more proptosis will be considered the primary study eye.

Efficacy will be evaluated by measurements of proptosis, plus both the 7-point Clinical Activity Score and CCI that encumbers both CCI and motility assessments.

Quality of life assessment will utilize the GO-QoL questionnaire.

Blood samples for linsitinib CCI
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Safety will be assessed through documentation of standard AEs, monitoring of concomitant medication use, physical and ophthalmic examinations, electrocardiograms (ECGs) vital signs, laboratory evaluations (chemistry, complete blood count, thyroid hormone levels, HbA1c, urinalysis and pregnancy testing). The study will also be monitored by a Data Safety Monitoring Board (DSMB).

Statistical Methods:

Sample size:

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Secondary endpoints will be tested in a hierarchical manner in the order specified below:

If the primary hypothesis is met, secondary endpoints will be tested in a hierarchical manner (in the order that follows):

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 Clinical Activity Scale (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 Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire overall score.

Safety Endpoints

All safety analyses will be performed using the Safety Population which will consist of all subjects who received at least one dose of study drug. Subjects will be analyzed according to the treatment that they received.

TEAE incidence (overall, as well as by severity, causality, and seriousness) will be tabulated by MedDRA system organ class and preferred term. Descriptive statistics will be used to summarize continuous laboratory parameters. Counts will be used for categorical lab parameters.

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

STUDY SCHEDULE OF ACTIVITIES

Table 1 Schedule of Activities

Schedule of Activities

Phase 2b Trial - Thyroid Eye Disease

Study Period	Screening	Baseline/ Randomization	Double-blind 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	W72/ET	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		
Opthalmologic exam[4]	X	X		X		X		X		X	X	X	X		X		
ECG/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 (HIV, Hep B, Hep C)	X																
Randomization via IRT and First Dosing		X															
Dispense study drug		<----------	----------	----------	----------	----------	----------	----------	----------	----------[12]							
Drug Reconciliation			<----------	----------	----------	----------	----------	----------	----------	----------[12]							
Clinical Activity Scale (CAS) [10]	X	X		X		X		X		X	X	X	X	X	X		
CCI																	
GO-QOL		X		X		X				X	X		X		X		
CCI																	
Adverse Events	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]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 (triplicate) ECGs at pre-dose, and hours 2, 3, and 4 post-dose. The subsequent visits at 3-week intervals will require one (triplicate) ECG. 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.

[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]ALT/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.

CCI [redacted]

[12]Arrows indicate drug dispensing and reconciliation. For more detailed information, please see the Pharmacy Manual.

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	adverse event
AKT	protein kinase B
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{\%extrap}$	percentage of $AUC_{0-\infty}$ extrapolated
AUC_{0-24}	AUC from time 0 to 24 h after dosing
AUC_{0-inf}	AUC over the dosing interval from time 0 to infinity
AUC_{0-last}	AUC over the dosing interval from time 0 to the last measurable concentration
BID	twice daily
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
C_{avg}	average concentration over the dosing interval
CL/F	apparent total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
C_{max}/D	dose-normalized C_{max}, calculated as the ratio of C_{max} to dose
CAS	Clinical Activity Score
COVID-19	coronavirus disease 2019
CQA	clinical quality assurance
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
CRA	clinical research associate
CSR	clinical study report
CCI [redacted]	
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation	Explanation
DSMB	data safety monitoring board
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
ET	Early Termination
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GO-QoL	Graves Ophthalmology Quality of Life
HA	Hyaluronic acid
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, and throat
hERG	human ether-à-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigator Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonization
ID	identification (number)
IEC	institutional ethic committee
IGF-1	insulin-like growth factor
IGF-1R	insulin growth factor-1 receptor
Phospho-IGF-1R	Phospho-insulin growth factor-1 receptor
IgG1	immunoglobulin G1
IL-6	interleukin-6
IL-16	interleukin-16
INR	international normalized ratio

Abbreviation	Explanation
IR	insulin receptor
IRB	institutional review board
λ_z	slope of the apparent elimination phase
LFTs	liver function tests, defined for this study as total bilirubin, ALT, AST, ALP, albumin, total protein, GGT, LDH
LDH	lactate dehydrogenase
LLN	lower limit of normal
µM	micromole
M22	Recombinant Human Antibody M22
MAPK/ERK	mitogen activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
ms	millisecond
nM	nanomole
NCI	National Cancer Institute
NHP	non-human primate
PBMC	peripheral blood mononuclear cells
CCI [redacted]	
qD	once daily
QoL	quality of life
QT interval	the time from the start of the Q wave to the end of the T wave
QTc	corrected QT interval
QTcF	QT interval corrected using the Fridericia method
RANTES	Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted
RNA	ribonucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvate transaminase

Abbreviation	Explanation
SOC	system organ class
$t_{1/2}$	apparent elimination half-life
TBL	total bilirubin
TED	Thyroid Eye Disease
TBD	to be determined
TBI	Thyroid blocking immunoglobulin
TEAE	treatment-emergent AE
TESAE	treatment-emergent SAE
Tg	thyroglobulin
T_{lag}	time prior to the first measureable (non-zero) concentration
T_{max}	time of maximum observed concentration
TMF	trial master file
TPO	thyroperoxidase
TSH	thyroid-stimulating hormone
TSHR	thyroid-stimulating hormone receptor
TSHRAbs	thyroid-stimulating hormone receptor autoantibodies
TSI	thyroid stimulating immunoglobulin
ULN	upper limit of normal
Vz/F	apparent volume of distribution based on the terminal phase calculated after a single extravascular administration where F (fraction of dose absorbed) is unknown
WOCBP	Women of Childbearing Potential

1. INTRODUCTION

1.1. Background

Thyroid eye disease (TED), also referred to as Graves' orbitopathy (GO) (ICD-10 H06.2) is a rare autoimmune condition with significant morbidity including orbital disfigurement, diplopia and even blindness that can have significant impact on quality of life (Ponto, 2009; Terwee, 2001; McKeag, 2007).

Studies show 85-90% of TED patients will develop, have concurrent or have had a recent history of Graves' Disease. Graves' Disease is an autoimmune condition that is caused by thyrotropin thyroid-stimulating hormone (TSH) receptor autoantibodies (TSHRAbs) that stimulates proliferation of thyrocytes and excessive autonomous secretion of thyroid hormone (hyperthyroidism). Studies show 10-15% of TED patients present with hypothyroidism or are euthyroid. TED manifests in a bimodal age distribution in females (40-44 years & 60-64 years) and males (45-49 years & 65-69 years). Risk factors for TED include smoking, presence of thyroid stimulating immunoglobulins (TSI) (the cause of Grave's Disease), hypercholesterolemia, prior I131 and treatment for hyperthyroidism. Female patients are 3 to 6 times more likely to be diagnosed with TED and male patients tend to present with a more severe form of the disease.

Clinically, TED is classified as two separate entities 1) active TED, lasting 1-3 years and manifesting earlier in the course of the disease with a marked autoimmune inflammatory response in the orbital tissue, or 2) inactive TED, characterized by a paucity of an inflammatory response and marked fibrosis. In Europe, the calculated combined prevalence active and inactive TED is approximately 10/10,000 individuals. (Perros, et al, 2015; Perros, et al, 2017) In an American Academy of Ophthalmology study of over 80,000 cases of TED, prevalence varied by ethnicity with the lowest prevalence in Hispanic highest prevalence in Black and intermediate prevalence in Asian or Pacific Islander, White and Other (Hyman, 2020). The only large-scale US population-based study on the epidemiology of TED, performed over 25 years ago, calculated an incidence rate of 1.6 cases/10,000 females/year, and .29 cases/10,000 males /year equating to an overall incidence of approximately 1/10,000 population. (Bartley, 1994) Due to the distinct pathology of active TED and the time limited nature of disease, active TED is markedly less prevalent that inactive TED. Approximately 35- 40% of the overall TED population has active TED (Perros, et al. 2015; Perros, et al, 2017). Importantly, moderate to severe active TED accounts for a third of all cases of active TED, equating to a USA incidence of moderate to severe TED of .34/10,000 (F: .53/10,000; M: .1/10,000) and a prevalence of less than 5/10,000 population. (Bartalena, et al, 2020; Lazarus, 2012; Chin, 2020; Bartley, 1994).

The pathogenesis of TED is intimately tied to the pathogenesis of autoimmune thyroid disease (i.e., Graves' Disease) in which pathogenic thyroid stimulating immunoglobulins (TSI) bind to the TSH receptor (TSHR) on the thyrocyte to stimulate excessive proliferation and thyroid hormone synthesis. (Bahn, 2010; Taylor, 2020). As in the hyperproliferative activation of the thyrocytes in Graves' Disease, the TSHR is also one of the primary autoantigens in TED, activated by the pathologic production of TSI. In TED however, the orbital fibroblast is the

target of TSI- mediated activation of proliferation, differentiation into adipocytes, the infiltration of immune cells into orbital soft tissues and the overproduction of pro-inflammatory cytokines (i.e., IL-6, TNF-α) and extracellular matrix components including the glycosaminoglycans chondroitin sulfate and hyaluronan. All contribute to edema and further increase in the volume of various orbital tissues that characterize the clinical manifestations of TED. Increasing evidence indicates that in TED, the insulin growth factor-1 receptor (IGF-1R) is the critical downstream effector of TSHR activation by TSI. The TSHR and IGF-1R physically and functionally interact to robustly activate downstream IGF-1R signaling pathways (that mediate the pathologic proliferation and differentiation (Lee, 2020; Neumann, 2020).

Current practice involves an assessment of the activity and severity of TED according to the well-established and standardized Clinical Activity Score (CAS). Disease is classified by a) Activity: inactive or active, and b) Severity: mild, moderate-to-severe or sight threatening. A determination of disease severity utilizes the CAS score and four other clinical parameters: soft tissue involvement as reflected CAS score, upper lid retraction, diplopia, proptosis, and clinical data indicating sight threatening complications. (Bartalena, et al, 2016).

Such assessment is critical in order to determine appropriate therapeutic strategy. A CAS score ≥ 4 out of 7 indicates active TED that can often be treated medically unless optic nerve or corneal ulceration necessitates surgery. Moderate-to-severe TED is defined by the presence of soft tissue swelling and pain, dry or red eyes, lid retraction and proptosis (exophthalmos). Sight-threatening complications of moderate-to-severe TED include optic neuropathy, corneal ulceration, and diplopia, all contributing to a significant decrease in quality of life (QoL) (Kahaly, 2020).

Mild active TED with normal or only minimally diminished QoL scan often resolves on its own or leaves minimal clinical sequela. For this reason, simple surveillance with no pharmacologic treatment is often an appropriate strategy. Moderate-to-severe active TED, on the contrary, requires medical management that at times includes acute or even urgent therapy. Until recently, high dose intravenous glucocorticoids have been considered front-line therapy (Bartalena, et al, 2020; Bahn, 2010; Bartalena, et al, 2016).

Pharmacologic doses of glucocorticoids (that act distal to the initiating IGF-1R signaling in TED orbital fibroblasts) decrease the synthesis and secretion of glycosaminoglycans from activated orbital fibroblasts. Pharmacologic doses of glucocorticoids also further serve as anti-inflammatory and immunomodulatory agents through the inhibition of the secretion of pro-inflammatory mediators and the subsequent recruitment of immunocompetent cells by directly suppressing B and T lymphocyte function (Taylor, 2020; Zang, 2011; Yang, 2014).

Orbital radiation and decompressive surgery are usually reserved for medically recalcitrant disease or emergent sight-limiting complications. Inactive TED therapies aim to reduce proptosis, correct lid retraction, strabismus, and any orbital disfiguration. These therapies are all suboptimal due to toxicities of long term pharmacologic glucocorticoid therapy and the risks and incomplete responses to surgical and radiotherapeutic approaches. As such the use of any treatment modality must be weighed against the inherent adverse effects (Yang, 2014; Lee, 2019; Wong, 2018; Boulanouar, 2020; Oeverhaus, 2017; Marcocci, 2003; Wakelkamp, 2004; Marquez, 2001; Bartalena, 2013).

Teprotumumab is a human immunoglobulin G1 (IgG1) monoclonal blocking antibody which binds to the membrane bound IGF-1R, blocks its activation and results in robust internalization and degradation of receptor. Developed as an anticancer agent, Teprotumumab was repurposed for use in TED based on preclinical data implicating the IGF-1R signaling pathway in the pathogenesis of TED as detailed above. Two multi-center randomized control trials with similar trial design of 24-week treatment and 48-week Follow-up were completed. The Phase 2 primary endpoint was set as a composite of reduction of at least 2/7 points in CAS and a reduction of at least 2mm in proptosis at week 24. The Phase 3 primary endpoint was set as a reduction in proptosis only. In both studies, approximately 70% of patients treated with teprotumumab (versus ~20% in placebo group) showed marked improvement in proptosis, CAS or both. While these results represent robust treatment effects, toxicities such as hearing loss (7%), nausea (20%) and muscle spasms (20%) together with the need to retreat a significant number of relapsing TED patients after 24 weeks of initial treatment, indicate the need for additional therapies and formal comparison to intravenous glucocorticoid therapy (Taylor, 2020; Douglas, 2020; Smith, et al, 2017).

1.2. Rationale for the Use of Linsitinib in Thyroid Eye Disease

The IGF-1R is a tetrameric transmembrane receptor tyrosine kinase widely expressed in normal human tissues and required for embryonic development and postnatal organ homeostasis in many organ systems. The receptor is activated following the binding of its cognate ligands, insulin-like growth factor-1 (IGF-1) and 2 (IGF-2) and by insulin at a much lower affinity (500- to 1000-fold less), activating intrinsic protein tyrosine kinase activity resulting in β subunit phosphorylation and the activation of downstream signaling. The genes coding IGF-1R and/or its ligands, IGF-1 and IGF-2 are amplified in a variety of human cancers where autocrine and paracrine activation of the IGF-1R stimulates proliferation, survival and angiogenesis in a variety of organ-specific cancers. Inhibition of IGF-1R by various approaches (including anti-IGF-1R antibodies and small-molecule inhibitors, antisense ribonucleic acid (RNA) and dominant-negative IGF-1R) has been shown to reduce tumor growth in human tumor xenograft model (Osher, 2019; Barlaskar, 2008; Fettig, 2020).

In addition to a pathogenic role of IGF-1R activation in neoplastic disease, multiple lines of evidence indicate that IGF-1R plays a critical role in regulating the pathologic proliferation and differentiation of orbital fibroblasts in TED. IGF-1R expression is increased in both lymphocytes and orbital fibroblasts from TED patients. In orbital fibroblasts, IGF-1R physically associates with the TSHR and IGF-1R signaling is activated through crosstalk after TSHR activation by TSI. A marked dysregulation of IGF-1R signaling is observed in microarray analysis of orbital fat from TED patients (Ezra, 2012). Recombinant IGF-1 and IgGs obtained from TED patients both result in increased hyaluronan synthesis and increased release of IL-16 and RANTES (Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted) from orbital fibroblasts of TED patients. The effect of TED IgGs are prevented by antagonists specific for IGF-1R (Smith, et al, 2016; Smith, et al, 2019; Smith, 2021).

Linsitinib

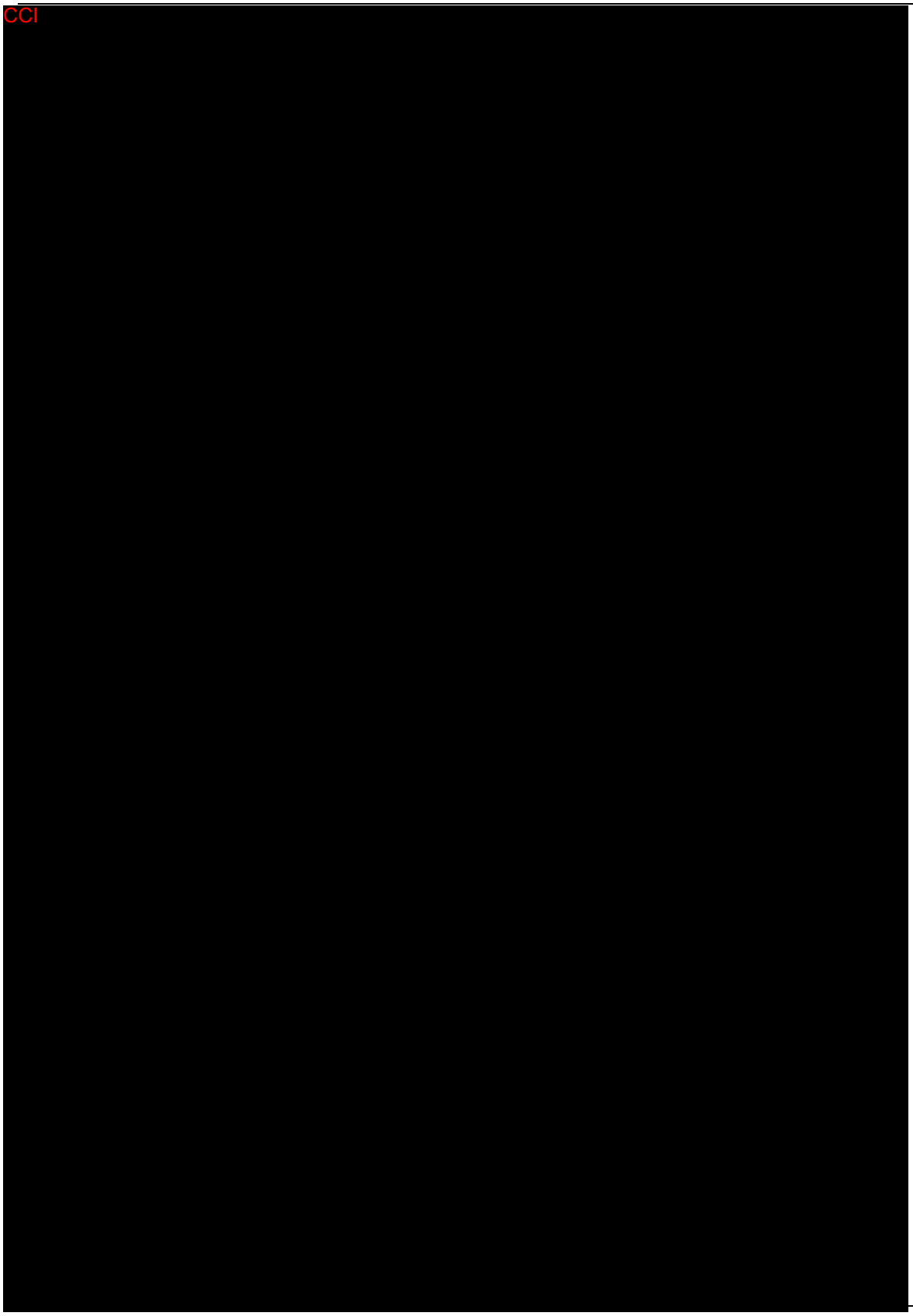
Linsitinib is a small molecule and a potent inhibitor of the in vitro tyrosine kinase activity of human IGF-1R, ligand-stimulated IGF-1R tyrosine kinase activity and IGF-1-stimulated protein kinase B (AKT) and mitogen activated protein kinase (ERK) signaling pathways. Linsitinib blocks IGF-1-stimulated receptor auto-phosphorylation and inhibits basal IGF-1R activity. Linsitinib inhibited growth of numerous types of human tumors. In particular, linsitinib has an EC50 of 0.54 μM (micromole) for inhibition of cell growth of H295R adrenocortical tumor cells and H295R cells exhibit a high level of activated IGF-1R and insulin receptor (IR), both of which are fully inhibited by linsitinib (Barlaskar, 2008; Mulvihill, 2009).

Moreover, linsitinib effectively inhibits HA secretion by TED orbital fibroblasts induced by both recombinant IGF-1, Recombinant Human **Antibody** M22 (TSHR stimulatory monoclonal antibody) or IgGs obtained from TED patients. In addition, in combination with TSHR antagonist (ANTAG3), linsitinib provides additive suppression of Hyaluronic acid **(**HA) secretion from TED orbital fibroblasts (Krieger, 2016; Place, 2017; Krieger, 2015).

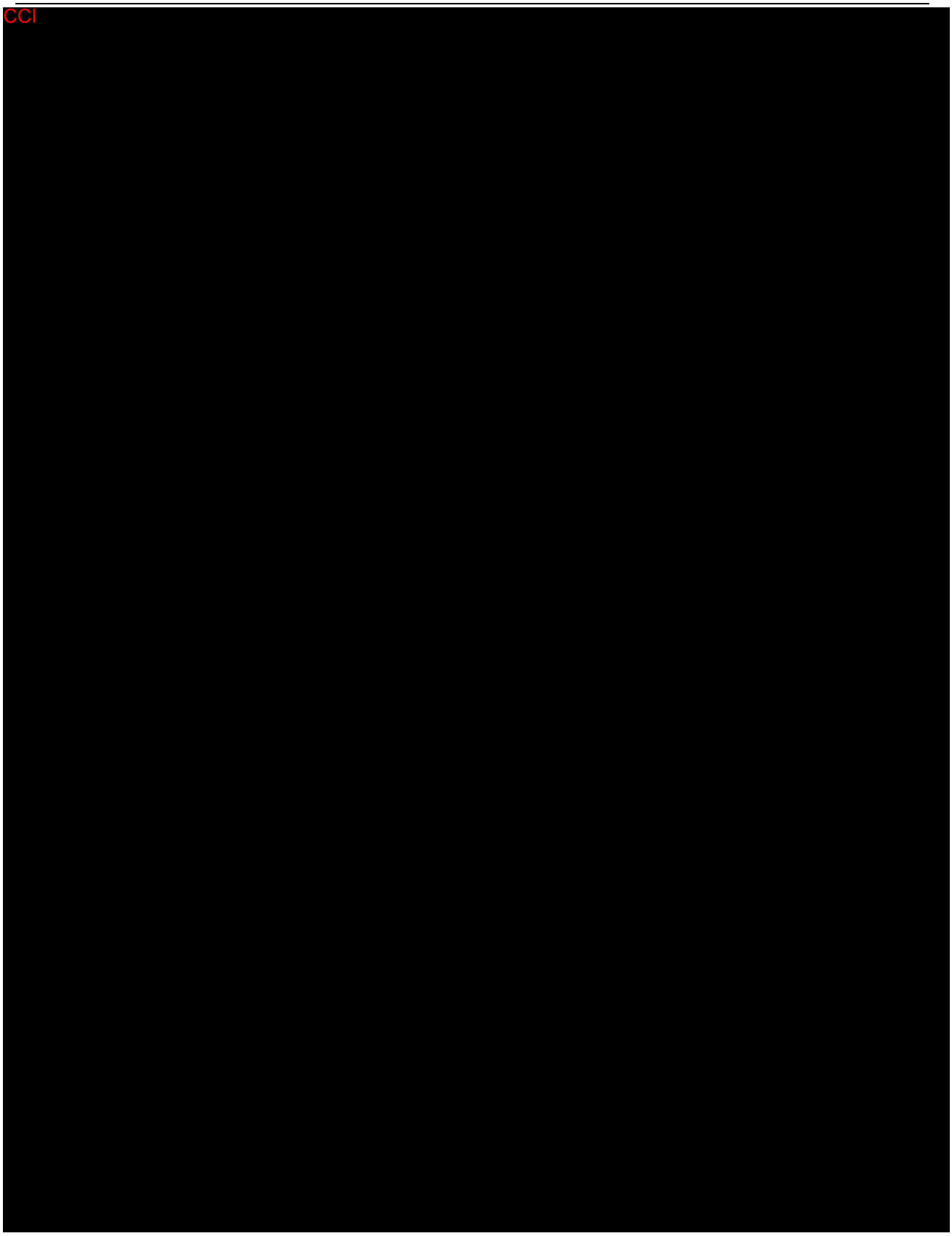
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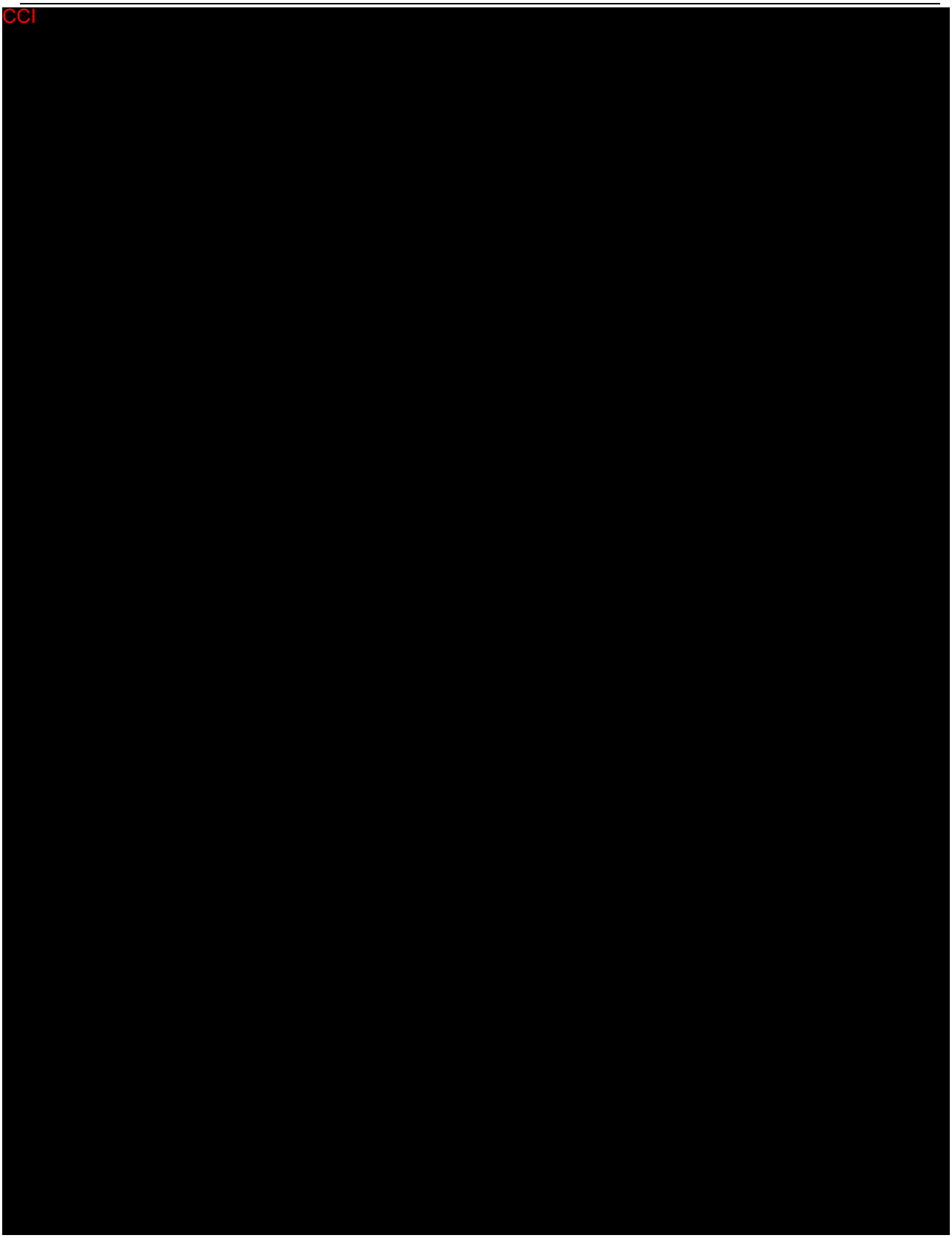
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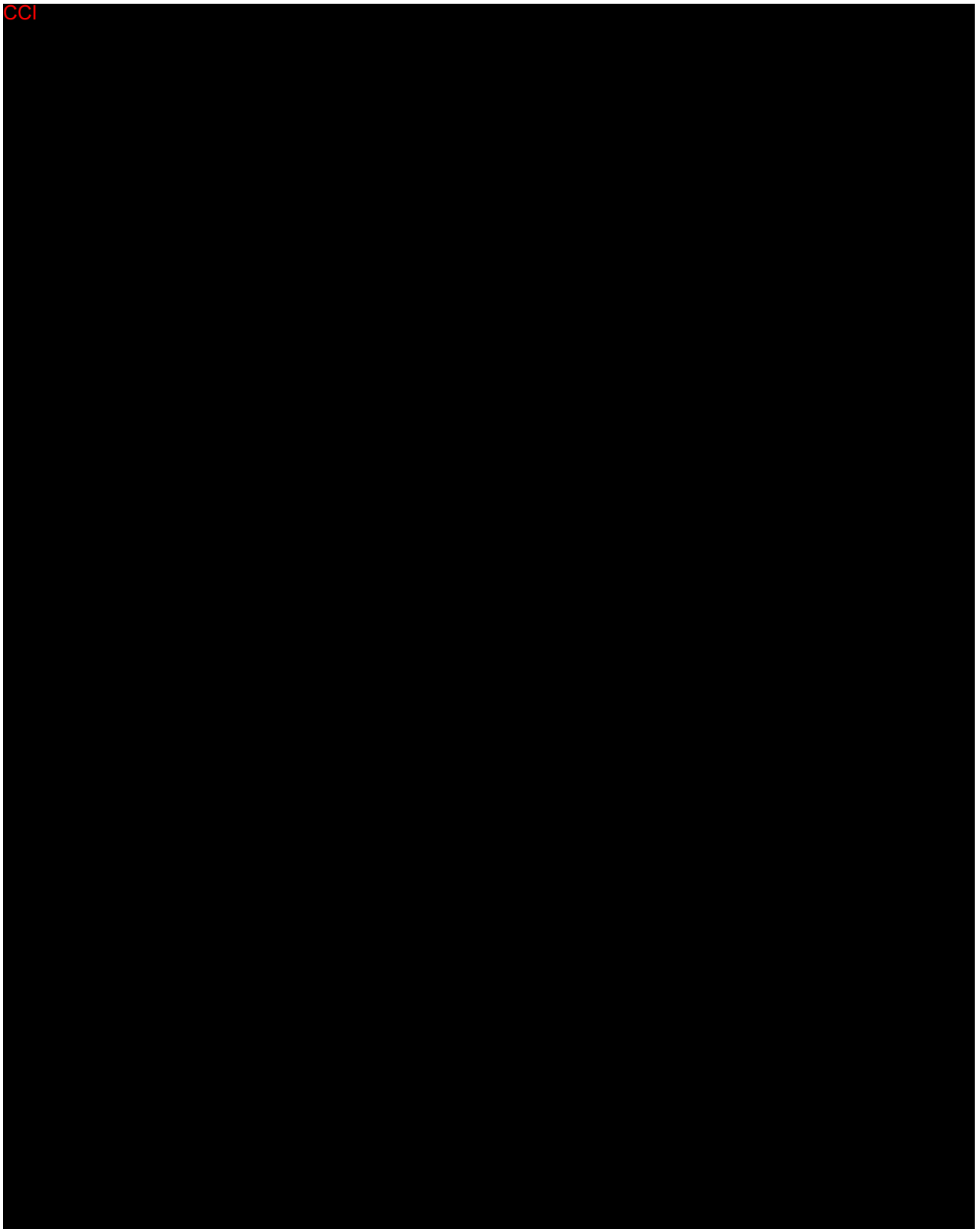
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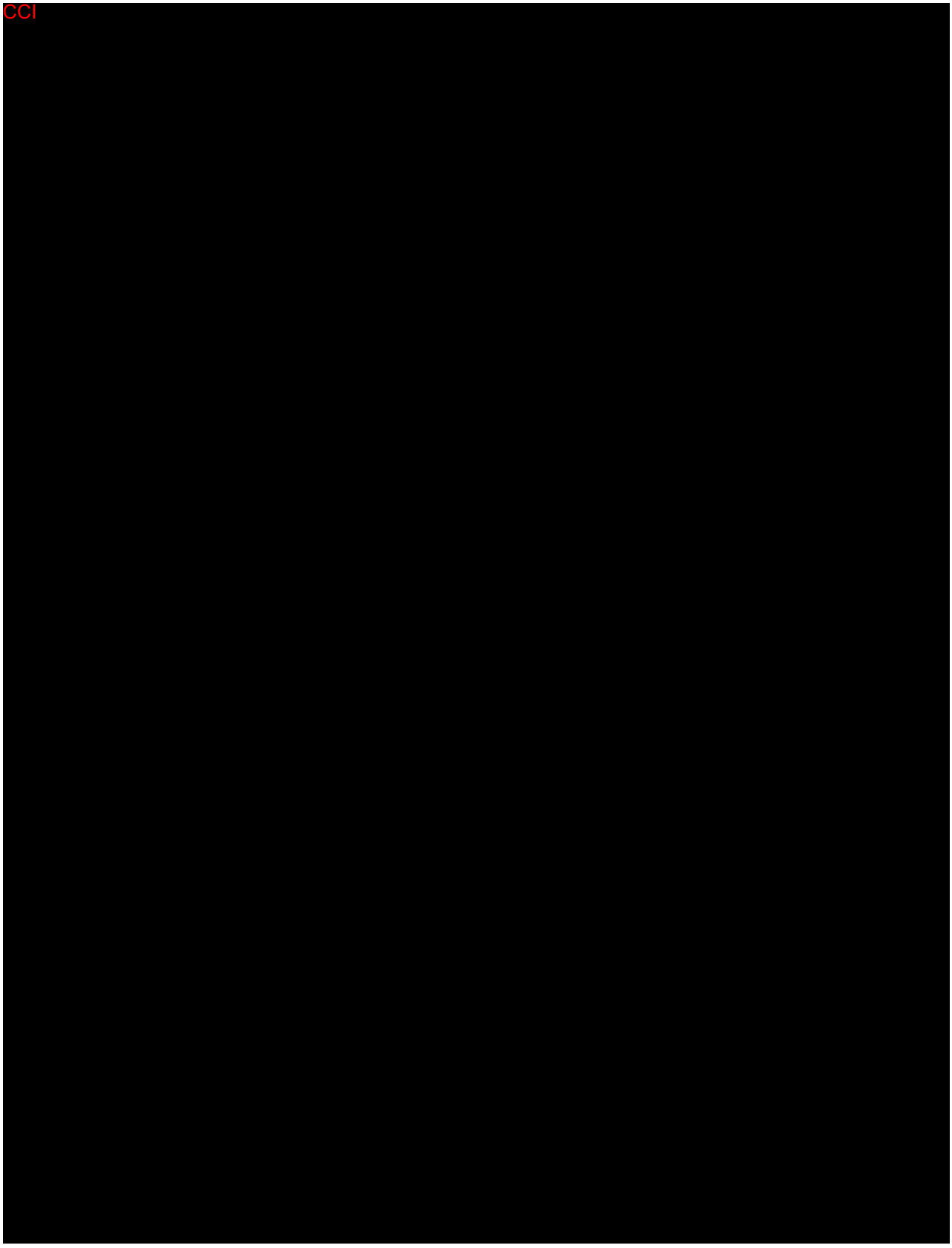
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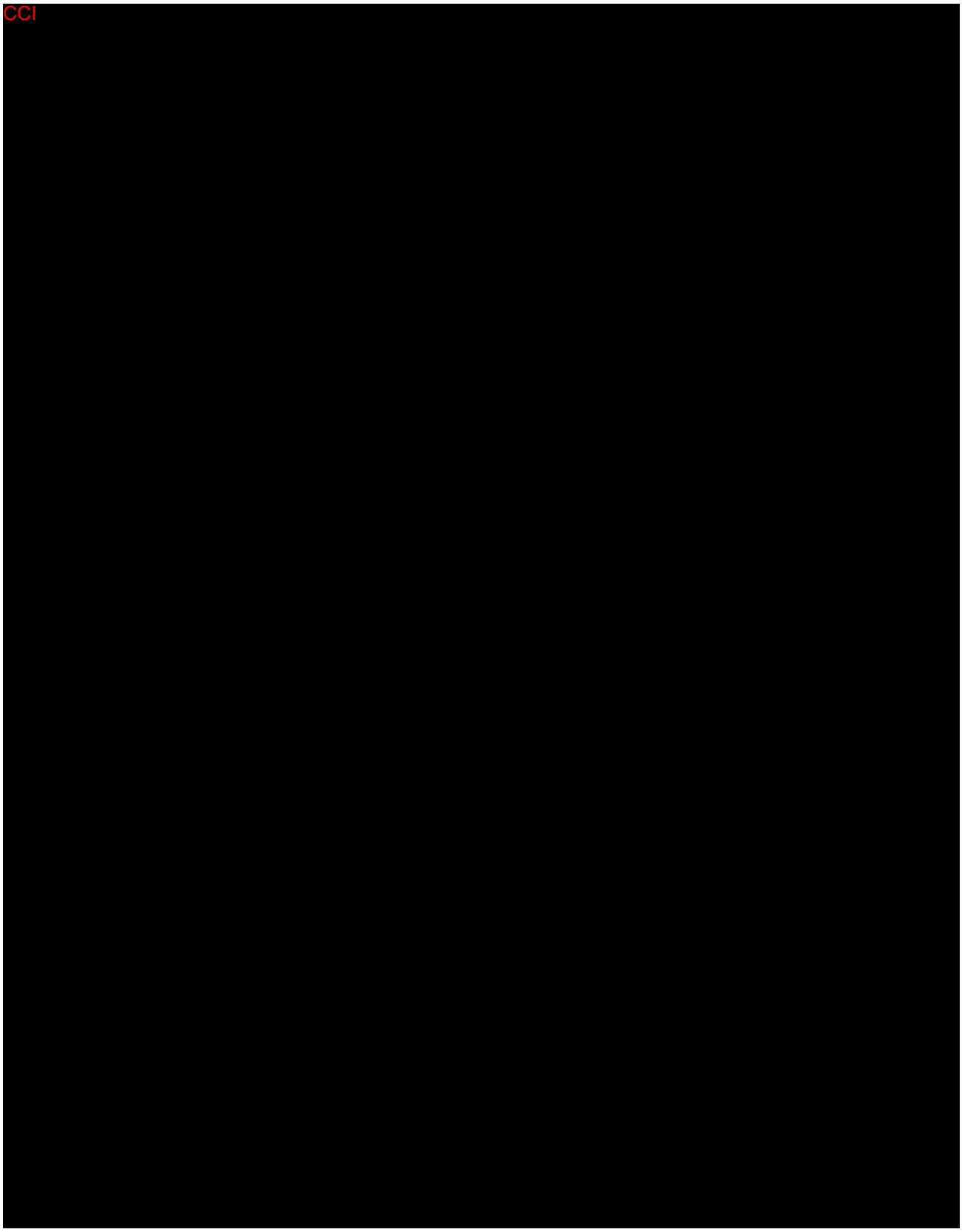
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2. STUDY OBJECTIVES AND PURPOSE

The primary objective is to study the safety, pharmacokinetics and efficacy of linsitinib in subjects with active, moderate to severe thyroid eye disease (TED).

2.1. Primary Objective

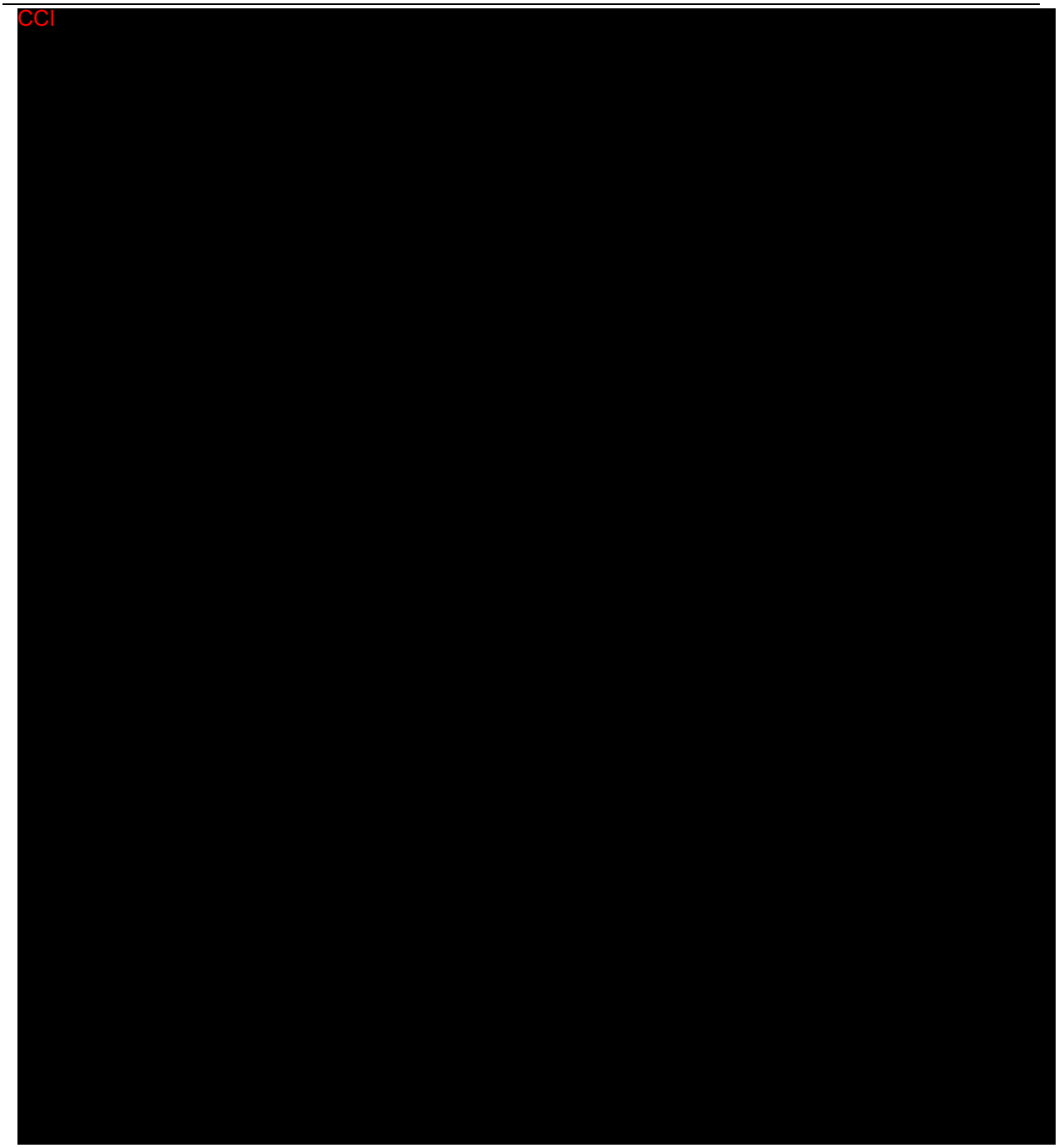
The primary objective is to study the effect of two doses of linsitinib versus placebo on the proptosis responder rate at Week 24. Responder rate is the percentage of subjects with a ≥ 2 mm reduction from Baseline in the primary study eye without deterioration (≥ 2 mm increase) of proptosis in the contralateral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

2.2. Secondary Objectives (analyzed hierarchically)

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 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.

2.3. Exploratory Objectives





2.4. Safety Objective

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

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

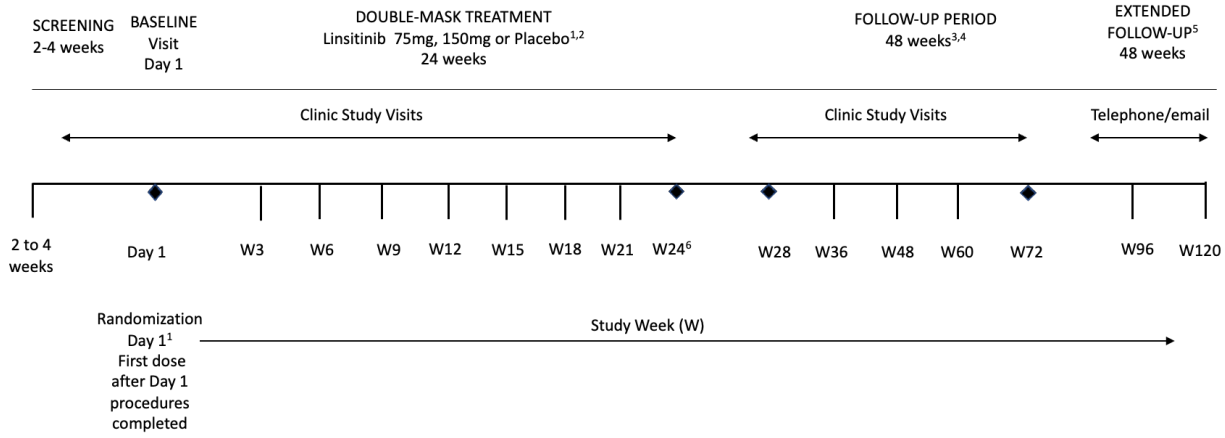
- Clinical safety laboratory results
- Vital signs
- Physical examination
- ECG parameters

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a phase 2b, double-mask, randomized, placebo controlled, multicenter, efficacy, safety and tolerability, CCI 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.

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.

3.2. Study Periods

3.2.1.1. Screening Period (Day -28 to Day -14)

After signing informed consent, subjects will enter a Screening period of 2 to 4 weeks' duration to assess eligibility for the study based on the inclusion and exclusion criteria. To assess eligibility, pertinent information will be collected, including demographic data including smoking status and childbearing potential, past medical and surgical history, physical

examination (including vitals, height, weight and BMI), ophthalmologic exam, prior and current medications and ECG/QT evaluation. Laboratory tests including serum pregnancy test, hematology, chemistry, urinalysis, cotinine (urine), fasting glucose, hemoglobin A1C, CCI [redacted] and viral screen (for human immunodeficiency virus (HIV), Hep B, Hep C) will also be obtained. The CAS and CCI including proptosis, CCI and motility restriction will also be administered.

3.2.1.2. Baseline and Randomization (Day 1)

Baseline information and tests will be completed prior to study randomization. Subjects will meet all inclusion and none of the exclusion criteria, and once complete, will begin Baseline study procedures prior to receiving study medication, including prior and concurrent medications and adverse events, physical exam (including vitals, weight/BMI), pretibial myxedema exam and ECG/QT evaluation test (pre-dose and hours 2, 3, and 4 post-dose). The efficacy assessments: CAS, CCI including proptosis, CCI and motility restriction, GO-QoL and ophthalmological exam will be completed. Laboratory urine pregnancy test, hematology, chemistry, urinalysis, fasting glucose, and CCI [redacted]

Subjects will remain at the clinic (within clinic/hospital grounds) for ECGs (in triplicate) at Day 1, pre-dose and hours 2, 3, and 4 post-dose with the ECG leads attached at the pre-dose timepoint and kept in place until after the 4-hour timepoint.

Following Baseline procedures, subjects will be randomized and given study medication and daily dosing instructions.

3.2.1.3. Treatment Period Study Visits (Weeks 3, 6, 9, 12, 15, 18, 21 and 24)

After initiation of study drug at the Baseline visit, study subjects will return to the clinic at scheduled times for clinic study visits. Subjects will be evaluated for efficacy assessments, physical and laboratory assessments, as well as undergo safety assessments per the study schedule of events (Table 1 Schedule of Activities).

Week 3 will have an ECG/QT evaluation test (in triplicate) at pre-dose and hours 2, 3, and 4 post-dose CCI [redacted]. Subjects will remain at the clinic (within clinic/hospital grounds) for ECGs at Week 3, pre-dose and hours 2, 3, and 4 post-dose with the ECG leads attached at the pre-dose timepoint and kept in place until the 4-hour timepoint. The subsequent visits at 3-week intervals will require one triplicate ECG and which will be reviewed by the reference laboratory.

3.2.1.4. Follow-up Period Study Visits (Weeks 28, 36, 48, 60 and 72)

A 48-week Follow-up period will occur immediately after the treatment period, with visits at Weeks 28, 36, 48, and 60 and 72. No study drug will be administered during this period. However, subjects will undergo an ophthalmologic exam and be assessed for safety, including the assessment of AEs, concomitant medications, ECGs, clinical laboratory tests, and vital signs per the study schedule of events (Table 1 Schedule of Activities).

If subjects meet the response criteria at Week 24 but subsequently experience a disease relapse during the 48-week Follow-Up Period, they will have the option to enter the VGN-TED-302 Extension Study if they meet criteria.

Relapse Criteria:

1. Increase in proptosis of ≥ 2 mm in the primary study eye since Week 24, or
2. An increase in CAS of ≥ 2 points since Week 24 with an absolute CAS of ≥ 4 in the primary study eye following the Week 24 Visit, and
3. In addition to one of the criteria above, the Investigator should also consider the subject's symptomology to ensure a relapse has occurred (e.g., new onset of double vision).

3.2.1.5. Extended Follow-up Period (Weeks 96 and 120)

Subjects who complete the Week 72 Visit are no longer restricted in their TED therapy and will be contacted 6 and 12 months later via phone or email by research staff (Week 96 and Week 120, respectively). Research Staff will enquire if any treatment for TED has been received since last study contact. If yes, subject will be questioned regarding type of treatment and outcome/response.

3.2.1.6. End of the Trial

The end of the trial is defined as the date of the last subject contact at Week 120.

3.3. Rationale for Study Design

Linsitinib is a small molecule and a potent inhibitor of the in vitro tyrosine kinase activity of human IGF-1R, ligand-stimulated IGF-1R tyrosine kinase activity and IGF-1-stimulated AKT and ERK signaling pathways. Linsitinib blocks IGF-1-stimulated receptor autophosphorylation and inhibits basal IGF-1R activity.

Linsitinib has been shown to effectively inhibit HA secretion by TED orbital fibroblasts induced by both recombinant IGF-1, M22 (TSHR stimulatory monoclonal antibody) or IgGs obtained from TED patients. In addition, in combination with TSHR antagonist (ANTAG3), linsitinib provides additive suppression of HA secretion from TED orbital fibroblasts (Krieger, 2016; Place, 2017; Krieger, 2015).

Following regulatory precedent and the mechanism of action of linsitinib, the primary objective is to study the 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.

The study is randomized in order to minimize bias in determining which subject receives which dose of linsitinib, or placebo. 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 study is placebo-controlled in order to have a comparison group to help determine whether safety findings during the study are related to the study drug and also to provide a true control rate for the assessment of efficacy.

3.4. Rationale for Dose Levels

Based on PK, PD and toxicology data in preclinical studies along with previous clinical observations in PK and PD responses and expected bioavailability, this data support the hypothesis that linsitinib will inhibit IGF1R in people with active, moderate to severe TED at doses of 75 mg BID, and 150 mg BID.

The known pharmacokinetic (PK) and pharmacodynamic (PD) properties of linsitinib were used to determine doses for the study of moderate to severe TED. The previous linsitinib clinical development program included PK along with assessments of IGF-1R/IR inhibition and IGF-1 levels at multiple doses. These biomarkers are known to be affected by the molecular pharmacology of linsitinib and such data informed the selection of doses for the planned TED clinical study, 75 mg BID and 150 mg BID. Considering PD, 150 mg BID consistently inhibited IGF1R and IR phosphorylation at trough plasma concentrations at steady stage. Single doses of 40-150 mg BID consistently increased IGF1 concentrations and were associated with C_{min} concentrations above 100 ng/mL. PK assessments found that consistent maintenance of 12-hour C_{min} at or above 100 ng/mL is likely to be achieved at 75 mg BID – but not at doses of 50 mg BID or lower. Consequently, the 75 mg BID and 150 mg BID dose regimens were selected to

enable evaluation of multiple linsitinib doses in TED with exposure ranges likely to inhibit the IGF1R target.

3.5. Study Duration

The planned study duration per subject is from 2-4 weeks screening, plus an additional 120 weeks.

3.6. Number of Subjects

The planned number of subjects is approximately 75.

3.7. Treatment Assignment

Eligible subjects will be randomly assigned to either linsitinib 75 mg BID or 150 mg BID, or placebo BID.

Changes in treatment are not permitted following randomization.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1. Inclusion and Exclusion Criteria

4.1.1. 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 participant's 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 study drug. It is recommended that hormonal (ie: 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 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 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.

4.1.2. 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 <1 g methylprednisolone or equivalent for the treatment of TED 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 steroids 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, 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 Medical 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 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) and TdP risk factors, e.g., hypokalemia and family history of Congenital Long QT syndrome.
18. Use of drugs potentially associated with 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. (Section 12.2)
19. *Removed due to amendment*
20. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal (ULN) according to age at Screening.
21. Serum creatinine > 2 x ULN for the reference range laboratory according to age at Screening.
22. 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.

23. Pregnant or lactating women.
24. 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.
25. 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.
26. Uncontrolled Human immunodeficiency virus (HIV), as judged by the Investigator, or positive hepatitis C, or hepatitis B.

4.2. Subject Withdrawal Criteria

In accordance with the Declaration of Helsinki and subsequent conferences, subjects have the right to withdraw from the study at any time for any reason. The Investigator and the Sponsor also have the right to withdraw subjects from the study. Subjects may be removed from the study for any the following reasons:

1. The subject experiences an AE that would preclude further treatment with the study drug.
2. The subject withdraws consent for continued participation or refuses further treatment with the investigational product.
3. The subject is noncompliant with the protocol.
4. The subject experiences persistent hyperglycemia that does not abate upon introduction of supportive measures, including standard of care for hyperglycemia (See Section 6.15). In case of fasting hyperglycemia > 250 (13.9 mmol/L), standard of care measures for hyperglycemia will be instituted and dosing may be interrupted at the discretion of the Investigator. Upon resolution of the blood glucose to < 160 mg/dL (8.9 mmol/L), study drug may be reintroduced. If study drug is not reinstituted within 3 weeks (i.e., next visit), the subject will be permanently discontinued from study. In addition, if a fasting hyperglycemia > 250 mg/dL (> 13.9 mmol/L) persists for more than 3 weeks without a documented fasting blood glucose ≤ 250 mg/dL (≤ 13.9 mmol/L), the subject will be permanently discontinued from study.

5. Study drug should be discontinued if the subject experiences persistent and/or significant increases in LFTs as detailed:
    - ALT or AST >8xULN
    - ALT or AST >5xULN for more than 2 weeks
    - ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
    - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- At the occurrence of isolated, asymptomatic elevations of AST or ALT >3xULN (not meeting above criteria) or AST or ALT ≤3xULN in individual subjects: continue linsitinib/placebo.
- At the occurrence of >3xULN LFT elevations: continue to monitor liver functions weekly until resolution to ≤3xULN or better and then according to protocol.
- At the occurrence of >5xULN elevations of AST or ALT in individual subjects: interrupt linsitinib/placebo until all hepatic toxicities improve. Reintroduce linsitinib/placebo when all hepatic toxicities have improved to ≤3xULN or better.
- Reintroduction of the study drug should not be allowed in case of toxicity of Grade ≥ 4.

6. Study drug dosing should be discontinued for any subject with a confirmed (repeated after > 1 minute) mean QTcF > 500 msec (> Grade 3), regardless of when the event occurs or causality. During the study, if the change-from-baseline QTcF is greater than 60 msec to a value greater than 470 msec, a repeat 12-lead ECG will be obtained as soon as practicable. In case the observation is confirmed, study drug dosing should be interrupted. Provided there is no significant cardiac toxicity (i.e., documented ventricular arrhythmia or syncope), study drug may be reintroduced upon resolution of the mean QTcF to < 470 msec (< grade 1).
7. In the Investigator's judgment, there is disease progression necessitating exclusionary rescue therapy (i.e., medication, surgery, or radiation).
8. Pregnancy (see Section 6.17.3)
9. Lost to follow up.
10. Study terminated by Sponsor

Subjects who discontinue study drug dosing prematurely during the double-mask treatment period will undergo Week 24 assessments and enter the Follow-up Period unless they initiated another intervention due to lack of efficacy. Subjects who prematurely discontinue during the Follow-up Period will undergo the Week 72 assessments. Subjects completing the Week 72 assessments will enter the Extended Follow-Up period. The reason for and date of withdrawal/removal from the study must be documented in the subject's medical records. Investigational site personnel must attempt to determine whether the reason for withdrawal was an AE and if so, this must be reported in accordance with the procedures provided in Section 6.16. TEAEs will be followed up until stabilization or resolution, in the opinion of the Investigator and the Medical Monitor. For all subjects who do not complete the study, regardless of the duration of treatment, all relevant information related to the withdrawal/removal will be entered into the electronic case report form (eCRF).

Subjects who withdraw or are removed from the clinical study after dosing will not be replaced. All randomized subjects will be fully accounted for and documented in the final CSR.

5. TREATMENT OF SUBJECTS

5.1. Assignment of Subject Identification Numbers

Once the subject has signed the Informed Consent Form (ICF) at Screening, site personnel will assign a subject identification number (ID). The subject ID will include a 3-digit site number and a 3-digit screen number, the latter assigned sequentially per site starting with 001.

Subject IDs will be utilized to identify the subject throughout the study. Each subject ID will only be assigned to one subject (e.g., if a subject is withdrawn from the study early, their subject ID will not be used for a new subject).

Each subject who qualifies for entry will be assigned a randomization number and corresponding treatment according to the randomization code. Inclusion and exclusion criteria will be reviewed by the Investigator, and only qualifying subjects will be enrolled into the study.

5.2. Description of Study Drug

The drug product formulation for this study is oral administration.

Table 3 Investigational Product

	Investigational Product	
Product Name:	Study Drug	Placebo
Dosage Form:	Tablet	Tablet
Unit Dose	75 mg	0 mg
Route of Administration	Oral	Oral
Physical Description	White round shaped, biconvex, film coated tablet	White round shaped, biconvex, film coated tablet that appear identical to study drug tablets
Manufacturer	CCI [redacted]	CCI [redacted]

For more information regarding linsitinib refer to the Investigator's Brochure.

5.3. Study Drug Packaging and Labeling

The formulation and bulk packaging of linsitinib will be conducted according to standard procedures.

The drug product will be packaged and labeled by the Sponsor's designated contract packager and labeller according to regulatory requirements.

5.4. Study Drug Storage and Accountability

Study drug must be kept in a secure location and stored at controlled room temperature (20°-25°C/68°-77°F) at the study site within its original container closure system. A daily temperature log for monitoring of proper storage conditions must be maintained by the site.

Access to study drug must be restricted to designated study personnel only. Under no circumstances should the Investigator or other site personnel supply study product to other Investigators or clinics or allow the supplies to be used other than as directed by this protocol. The Investigator (or designee) must maintain records of the delivery of the study drug to the study site, the inventory at the study site, use for each subject and return of the study drug to a designee of the Sponsor for destruction, if applicable. Total study site accountability will be conducted throughout and at the end of the study and the Investigator must explain all discrepancies. A site drug accountability log must be kept current and will contain information such as:

- Identification (subject ID) of the subject to whom the study drug is dispensed
- The dates and bottle numbers for the dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor. Additional details on the storage and handling of linsitinib are provided in the Pharmacy Manual.

5.5. Study Drug Administration

5.5.1. Dosing and Administration

Subjects will receive twice daily doses of linsitinib or matching placebo, 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. Additional details are described in the Pharmacy Manual.

5.6. Study Drug Compliance

Initial and daily dosing regimen will be explained with subjects on Day 1 in the clinic. The investigational product will be exclusively dispensed by qualified personnel at the study site and only to subjects randomized into the study.

The time of administration should be recorded for doses taken while the subject is in the clinic. Thereafter, study doses will be taken at home twice per day 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 CCI [redacted] while in clinic. Last dose of study medication is taken the evening prior to the Week 24 visit.

5.7. Study Medication and Management for Toxicity

Study drug dosing should be interrupted if a subject experience > Grade 3 clinically significant toxicity related to study drug (additional reference Section 4.2 Subject Withdrawal Criteria). Upon resolution of the toxicity to < Grade 1 or no more than 1 Grade above baseline, study drug may be reintroduced. Reintroduction of the study drug should not be allowed in case of toxicity of Grade ≥ 4.

5.8. Randomization and Masking

All subjects will be randomized to receive either 75 mg BID or 150 mg BID linsitinib or matching placebo (n=25 per group). The randomization scheme is 1:1:1 (75 mg BID linsitinib:150 mg BID linsitinib: placebo).

The randomization list will be kept in a secure location until after database lock and extraction of data. However, the treatment assignment for an individual subject will be provided if unmasking is necessary for a SAE. Further details are provided in the RTSM Site User Guide.

5.9. Study Drug Handling and Disposal

At the time of study close-out, the Sponsor will direct the site regarding the disposition of any unused study drug, i.e., whether it is to be destroyed or be returned to the Sponsor's designated location. Further details are provided in the Pharmacy Manual.

5.10. Concomitant and Restricted Medications

Use of concomitant medications should be kept to a minimum during the study. However, if concomitant medications are considered necessary for subject welfare and are unlikely to interfere with the investigational product, they may be given at the discretion of the Investigator. During the study and within 6 months prior to Screening, any medication given other than the study drug (including blood transfusions, parenteral fluids, over-the-counter medications, and herbal preparations) is to be considered a concomitant medication and must be documented on the eCRF.

5.10.1. Permitted Concomitant Medications

Supportive Medications: Supportive measures including analgesics (e.g., non-steroidal anti-inflammatory therapies, acetaminophen), and supplements/medications for conditions other than TED are permitted during the study. Inhaled corticosteroids are allowed.

Antihyperglycemic Medications:

Supportive measures including standard of care for hyperglycemia will be introduced at the Investigator's discretion (see Section 6.15).

Treatment of emergent toxicities is at the investigator's discretion.

5.10.2. Restricted Medications and Therapies

Restricted medications and therapies are listed in Table 4 below.

Table 4 Restricted Medications and Therapies

Medication/Therapy	Restricted Dose and Time Period
Orbital surgery and orbital irradiation	Any history or planned procedure from Screening through Week 72 of Follow-up Period.
Ocular surgery and other ophthalmological interventions	Any history (see Exclusion 15), or planned procedure from Screening through Week 72 of Follow-up Period.
Glucocorticoids for treatment of TED	Any glucocorticoid use (IV or oral) with a cumulative dose equivalent to ≥ 1 g of methylprednisolone or equivalent for the treatment of TED within 3 months of Screening through Week 72 of Follow-up Period. Previous glucocorticoid use (IV or oral) with a cumulative dose of <1 g methylprednisolone or equivalent for the treatment of TED and previous use of steroid eye drops is allowed if discontinued at least 4 weeks prior to Screening and should not be initiated through Week 72 of Follow-up Period.
Glucocorticoids for conditions other than TED	Oral or IV glucocorticoid use for conditions other than TED is allowed if discontinued at least 4 weeks prior to Screening and should not be initiated through Week 72 of Follow-up Period. Topical steroids for dermatological conditions and inhaled steroids are allowed. Intra-articular steroids are allowed if discontinued at least 4 weeks prior to Baseline and should not be given during the study prior to Week 24.
Non-steroid eye drops	Dilating eyedrops (e.g., including phenylephrine) are allowed for eye exams if ophthalmologist judges that a dilated fundus examination is indicated. Vasoconstrictor eye drops are not allowed during the study. Other non-steroid drops such as saline or methylcellulose are allowed but should not be used on the day of a study visit.
Selenium or biotin	3 weeks prior to Baseline through Week 72 of Follow-up Period. A multivitamin containing selenium and/or biotin is allowed during the trial.

QT Prolonging drugs	14 days prior to Day 1 dosing through Week 72 of Follow-up Period (See Section 12.2)
Previous treatment	Any previous treatment with anti-IL6 receptor, anti- CD20, (MS4A1) antibodies or monoclonal antibody for immunomodulation prior to Screening through Week 72 of Follow-up period.
Non-steroid immunosuppressive agent	Any non-steroid immunosuppressive agent use within 4 weeks prior to Screening through Week 72 of Follow-up Period.
Investigational agent	30 days prior to Screening through Week 72 of Follow-up Period.
Illicit drug/alcohol use	Current drug, marijuana or alcohol abuse within the past 1 year through Week 72 of Follow-up Period.

5.11. Potential for Drug Interactions

CYP1A2 and CYP2C9 inhibitors/inducers: Linsitinib is primarily metabolized by CYP1A2; therefore, a potential for drug-drug interaction exists when linsitinib is co-administered with drugs that are CYP1A2 inhibitors/inducers. While CYP1A2 inhibitors/inducers are not specifically excluded, investigators should be aware that linsitinib exposure may be altered by the concomitant administration of these drugs.

Linsitinib is a moderate inhibitor of CYP2C9. While CYP2C9 substrates are not specifically excluded, investigators should be aware that levels of drugs metabolized by CYP2C9 may be increased by the concomitant administration of linsitinib. Caution should be used when administering CYP2C9 substrates to subjects who are on study drug.

For ECG/QT information, please refer to Section 6.9 Electrocardiography and Determination of QTc and Section 12.2 List of QT Prolonging Medication.

6. STUDY PROCEDURES

6.1. Allowable Variation in Time of Procedures

Visit time points are intended as targets and variations may be made to allow for logistical considerations and to accommodate scheduling conflicts. Please see Table 1 Schedule of Activities for allowed procedure and visit windows. The Medical Monitor or appropriate designee should be contacted to discuss any procedures that are anticipated to occur outside of the allowed windows.

6.2. Informed Consent

Prior to any study-specific screening evaluations and clinical trial participation, written informed consent will be obtained from each subject to be involved in the clinical trial by using the Institutional Review Board (IRB)/ institutional ethic committee's (IEC) approved ICF. Through the ICF, potential subjects will be informed in detail about the study drug and the nature of the clinical investigation with the risks and discomforts to be expected.

The approved ICF provided to the subject shall be in language understandable to the subject and updated whenever new important information is available or when protocol amendments occur which requires an updated consent. When amendments occur or updated information is available the Investigator will discuss with these changes/updates as soon as possible subject and reconfirm the subject's participation in the study by their signature on the amended written informed consent.

The subjects will also be instructed that they are free to withdraw their consent and discontinue their participation in the clinical study at any time. The Investigator or qualified designee will verify that the subject has granted consent. Each subject will be given a copy of the signed ICF. Certified translated ICFs will be provided by the Sponsor in those languages required or requested by investigational sites.

6.3. Eligibility

Review of all relevant study inclusion/exclusion criteria will be done during Screening, at the beginning of the Baseline visit, and before randomization into the Double-mask Treatment Period.

6.4. Determination of Primary Study Eye

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.

6.5. Demographics and Medical History

Demographic information including smoking status, and childbearing potential will be collected at Screening.

A complete medical history will be obtained at the screening visit, including a review of the head, eyes, ears, nose and throat (HEENT), respiratory, cardiovascular, gastrointestinal, hepatobiliary (specifically, a history of liver dysfunction or the presence of hepatomegaly or splenomegaly), genitourinary/reproductive, for women includes menopausal history and screening, musculoskeletal, neurological, psychiatric, endocrine/metabolic, blood/lymphatic, dermatologic and immunologic systems. Past surgeries will also be recorded.

6.6. Prior and/or 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. In addition, records should include any use of prohibited or restricted medications (Section 5.10.2)

6.7. Vital Signs, Height, Weight and Body Mass Index (BMI)

Vital signs (temperature, systolic and diastolic blood pressure (BP), heart rate (HR), and respiratory rate) and weight/BMI will be measured at Screening, the Baseline visit and during all Double-mask Treatment Period visits, Follow-up Period visits, and End of Study visit.

Systolic and diastolic BP should be taken in the same arm as much as possible per subject after the subject has been sitting for at least 5 minutes. Any clinically necessary deviations to this will be documented but do not need to be confirmed with the Medical Monitor prior to occurrence or documented as a protocol deviation.

Height will be measured only at Screening.

6.8. Physical Examination

A complete physical examination will be performed at Screening, Baseline and during the Double-mask Treatment Period on Weeks 6, 12, 18, and 24, and Follow-up Period Weeks 48 and 72. During the Double-mask 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.

6.9. Electrocardiography and Determination of QTc

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). Hourly ECG measurements should be performed with a window of +/- 5 minutes. ECG measurements, PK and PD draws for these timepoints, should be completed within a 15-minute timespan.

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.

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.

Subjects will remain at the clinic (within clinic/hospital grounds) for ECGs at Day 1 and Week 3, pre-dose and hours 2, 3, and 4 post-dose with the ECG leads attached at the pre-dose timepoint and kept in place until the 4-hour timepoint.

The ECG tracings will be interpreted by usual clinic procedures and ECG findings will be sent to a central reader for analysis. ECGs will be stored for later analysis if needed.

For all ECGs, the QT interval will be corrected using the Fridericia method ($QTcF = QT/RR^{0.33}$). If QTcF is greater than 450 msec for males and 470 msec for females on the Screening (Visit S1) ECG, three consecutive ECGs will be obtained and the QTcF values will be averaged. If the average is greater than 450 msec for males and 470 msec for females, the subject will be ineligible for the study.

Study drug dosing should be discontinued for any subject with a confirmed (repeated after > 1 minute) mean QTcF > 500 msec (> Grade 3), regardless of when the event occurs or causality.

During the study, if the change-from-baseline QTcF is greater than 60 msec to a value greater than 470 msec, a repeat 12-lead ECG will be obtained as soon as practicable.

In case the observation is confirmed, study drug dosing should be interrupted. Provided there is no significant cardiac toxicity (i.e., documented ventricular arrhythmia or syncope), study drug may be reintroduced upon resolution of the mean QTcF to < 470 msec (< grade 1).

Additional ECG instructions are located in the ECG Manual. Any subject with notable results will be asked to return to the clinic within 3 days for evaluation and repeat ECG testing. If QT prolongation or other notable effects remain, the subject will undergo EOT procedures and be terminated from the study.

6.10. Pretibial, Myxedema Exam

Pretibial myxedema will be assessed on Baseline/Day 1, Week 24 of the Double-mask Treatment Period, and Week 72 of the Follow-up Period. Measurements will be taken of calf circumference and instep if pretibial myxedema is observed.

6.11. Ophthalmologic Exam

An ophthalmologic examination will be completed at Screening, Baseline/Day 1, during the Double-mask Treatment Period study visits at Weeks 3, 6, 12, 18, 24 and in the Follow-up Period Weeks 28, 36, 48 and 72 (Section 12.4).

Ophthalmologic exams will include 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.

Subjects who have decreased best-corrected visual acuity due to optic neuropathy (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) at Screening are not eligible for enrollment. New findings reported from on-study ophthalmic examinations will not be reported as AEs if, according to the Investigator, the abnormalities are TED specific disease manifestations.

6.11.1. Proptosis Assessment

Proptosis is evaluated during the CCI assessment. The Hertel exophthalmometer will be used to assess proptosis throughout the study. A Hertel exophthalmometer will be provided by Study Sponsor for these measurements. Please see Section 12.4 for examination details.

6.11.2. Motility Assessment

Motility in vertical and horizontal gaze is evaluated during the CCI assessment and will be determined using the light reflex (LR) test. [Dolman et al, 2012]. Motility can be graded from 0º to 45º in four directions using the Hirschberg principle: The subject will be asked to look as far as possible up, down, right, and left 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 30º; if the light reflex hits the limbus, the eye has rotated 45º. Intermediate ductions will be judged by estimating the light position between these points to the nearest 5°. The monocular ductions of each eye (in degrees) will be recorded for adduction, abduction, supraduction and infraduction. Except when unavoidable, the same observer should conduct each duction evaluation throughout the study. The four values (in degrees) for the primary study eye are summed for each subject.

CCI

Subjective diplopia score:

CCI

[redacted]

6.12. Clinical Activity Score (CAS)

The CAS will be completed at Screening, Baseline/Day 1 and Weeks 6, 12, 18, and 24 during the Double-mask Treatment Period, and at Weeks 28, 36, 48, 60, and 72 during the Follow-up Period using the 7-item European Group on Graves' Ophthalmopathy (EUGOGO) amended CAS [Mourits, et al, 1997] (Table 5).

The CAS must be ≥ 4 for enrollment and randomization. Subjects whose CAS score decreases 2 or more points from Screening to Baseline are not eligible for randomization.

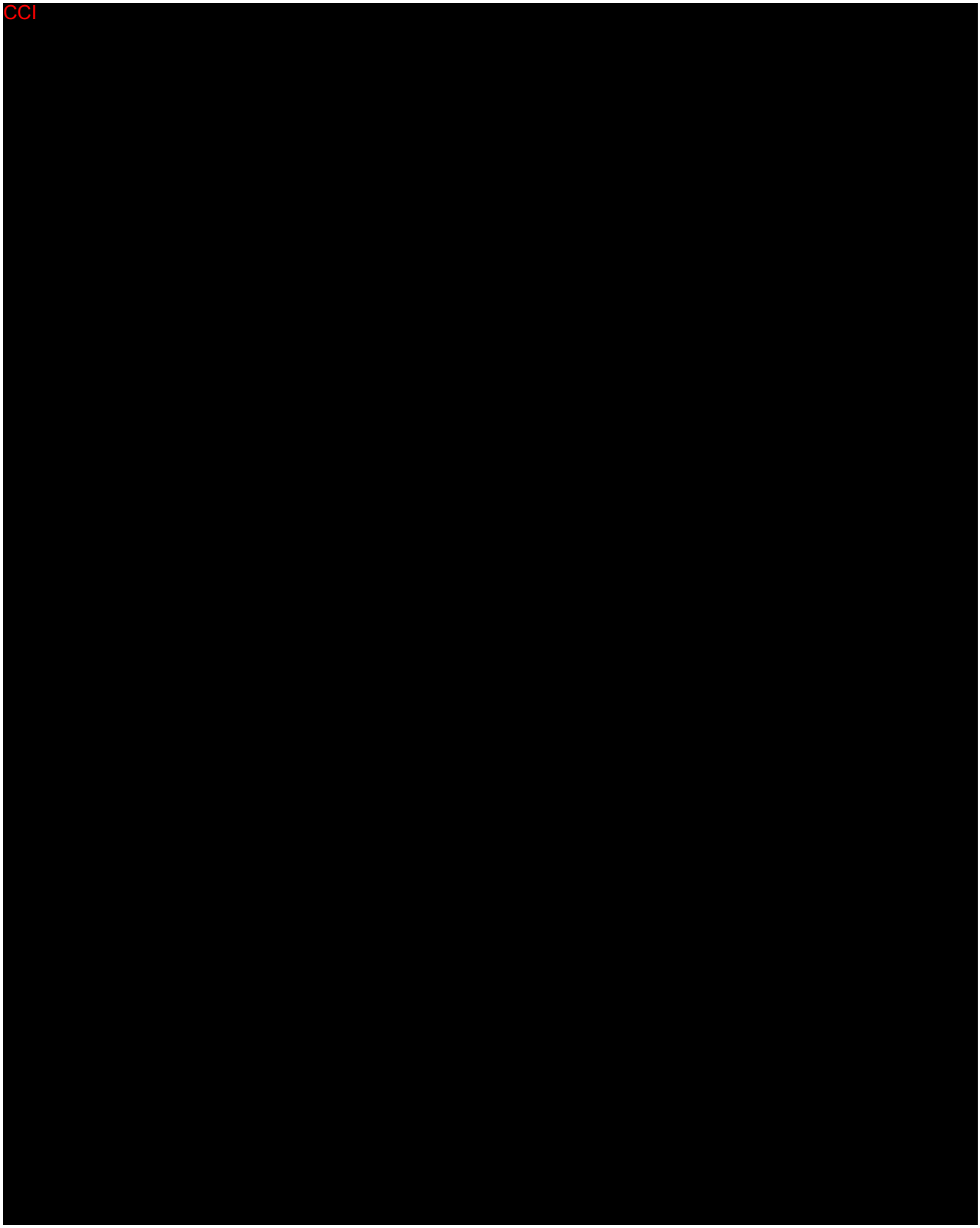
All Investigators will be trained and provided the Clinical Manifestations chapter in Graves' Orbitopathy: A Multidisciplinary Approach – Questions and Answers [Dickinson, 2010] to support consistency in data collection across study sites. The same reviewer should conduct each CAS evaluation for the full duration of the study, except when strictly unavoidable.

Table 5 Clinical Activity Score

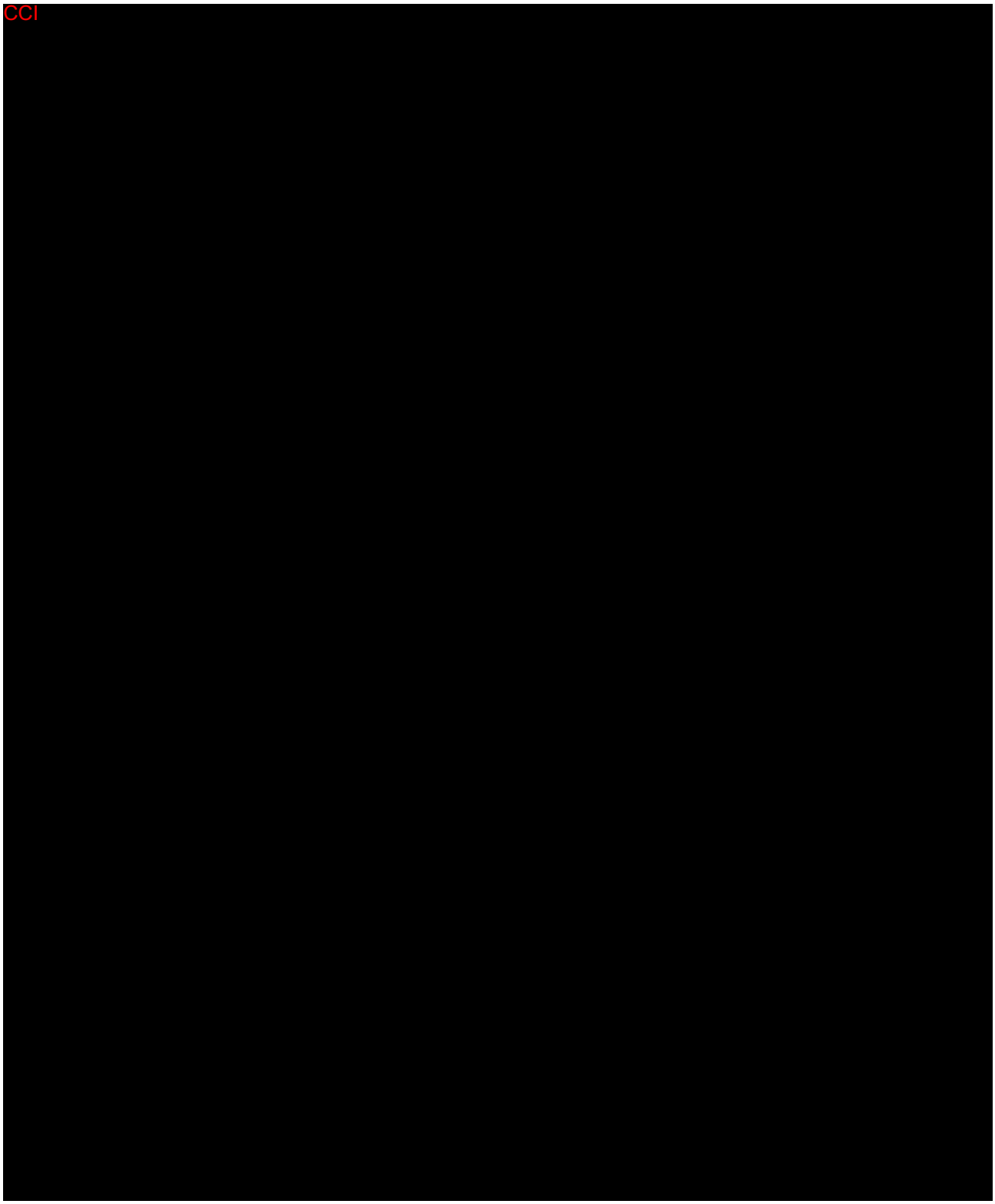
Description of Sign/Symptoms[1]
1. Spontaneous retrobulbar pain.
2. Pain on attempted upward or downward gaze
3. Redness of eyelids
4. Redness of conjunctive (due to active TED/GO associated-inflammation)
5. Swelling of caruncle or plica
6. Swelling of eyelids (due to active TED/GO associated-inflammation)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

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

CCI



CCI



6.14. GO-QoL Questionnaire

Subjects will complete the Graves' Ophthalmology Quality of Life Questionnaire (GO-QoL) at Baseline/Day 1 and Weeks 6, 12 and 24 during the Treatment Period, and at Weeks 28, 48 and 72/Early Termination during the Follow-up Period (see questionnaire in Section 12.3).

Designed to assess the perceived effects of TED on subjects, the GO-QoL (Terwee, et al, 1998, Terwee, et al, 1999) is a simple questionnaire (16 items) divided into 2 sections that surveys both a) daily physical activity and 2) psychosocial function - pertinent to visual function.

Responses to GO-QoL will be utilized to generate pre-specified QoL scores as defined in the GO-QoL scale. Descriptive summaries for responses of each subject at Baseline and over time will be assembled in appropriate tables. Using the MMRM model described, an overall score together with the VF and A subscale scores will be determined at Week 24. Final analysis plans will be provided in SAP.

6.15. Hyperglycemia Evaluation

Subjects with diabetes mellitus can participate in this study, on the predicate that the disease is "controlled" as defined. HbA1c levels will be assessed regularly in these subjects, as defined in the Schedule of Events. HbA1c must be < 9.0% for randomization. Investigators are encouraged to maximize glycemic control to maintain subjects' HbA1c levels <9% throughout the study period. When a subject's HbA1c level rises to >9% at any time point after Screening, the Investigator is required to assess the risk versus benefit of remaining in the study. Moreover, if the HbA1c rises to >9% and considered clinically significant at any time point after Screening, it will be repeated approximately every 45 days until it returns to a value within the normal range.

For non-diabetic subjects, fasting blood glucose levels (after at least an 8-hour fast) will also be obtained at Screening and Day 1. For diabetic subjects, fasting blood glucose levels will be obtained at every visit as specified in the schedule of activities during the Treatment and Follow-up Periods.

In subjects who demonstrate hyperglycemia (defined as a fasting blood glucose >126 mg/dL) in diabetic subjects or a nonfasting blood glucose ≥200 mg/dL in nondiabetic subjects) during the treatment period, a critical element in the medical management is to obtain a repeat serum fasting glucose (for diabetics and nondiabetics) to confirm the finding and monitor until a normal blood glucose level is achieved.

Supportive measures including standard of care for hyperglycemia will be introduced at the Investigator's discretion. In case of fasting hyperglycemia > 250 mg/dL (> 13.9 mmol/L), standard of care measures for hyperglycemia will be instituted and dosing may be interrupted at the discretion of the Investigator. Upon resolution of the blood glucose to < 160 mg/dL (8.9 mmol/L), study drug may be reintroduced. If study drug not reinstituted within 3 weeks (i.e., next visit), the subject will be permanently discontinued from study. In addition, if a fasting hyperglycemia > 250 mg/dL (> 13.9 mmol/L) persists for more than 3 weeks without a

documented fasting blood glucose ≤ 250 mg/dL (≤ 13.9 mmol/L), the subject will be permanently discontinued from study.

6.16. Adverse Events, Serious Adverse Events and Reporting

6.16.1. Definition of Adverse Event, Adverse Drug Reaction and Unexpected Adverse Drug Reaction

Adverse Event (AE): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

New findings reported from on-study ophthalmic examinations will not be reported as AEs if, according to the Investigator, the abnormalities are TED specific disease manifestations (See Section 6.11).

- All AEs, regardless of relationship to study drug, should be collected beginning from the time the subject signs the ICF through the Follow-up period. (Any SAE judged by the Investigator to be related to the study drug should be reported to the Sponsor regardless of the length of time that has passed since study completion.) AEs in study subjects include any change in the subject's condition. This includes symptoms, physical findings, or clinical syndromes.
- Wherever possible, a specific disease or syndrome, rather than individual associated signs and symptoms, should be identified by the Investigator and recorded. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure. Any medical condition already present at Screening should not be reported as an AE unless the medical condition or signs or symptoms present at Baseline worsens in severity or seriousness at any time during the study. Clinically significant examination findings that are detected during the study or are present at Screening and worsen during the study should be reported as an AE.
- An abnormal laboratory value may be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not. It is up to the Investigator to determine whether an abnormal laboratory value constitutes an AE. If an abnormal laboratory value is caused by a disease process, the disease process and not the laboratory abnormality should be listed as the AE (e.g., if new onset viral hepatitis is causing elevated ALT, hepatitis and not the elevated ALT should be listed as the AE).
- Examples of laboratory abnormalities that should be considered AEs include those that result in withdrawal of the study drug, withholding study drug pending some investigational outcome, or additional concomitant treatment. All laboratory abnormalities considered to constitute an AE should be recorded on the appropriate AE

page of the eCRF. Laboratory abnormalities do not need to be listed as separate AEs if they are considered to be part of a clinical syndrome that is being reported as an AE. It is the responsibility of the Investigator to review all safety laboratory findings in all subjects. Abnormal values should be commented upon as to clinical relevance or importance on the eCRF or the laboratory report as appropriate. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Laboratory evaluations at all visits will be following National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Guidelines and definitions (Version 5.0 November 27, 2017).

(https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)

- Investigator must categorize each AE according to its severity and its relationship to study drug.
- Subjects who develop adverse events while on study should be followed until the event resolves, stabilizes or returns to baseline.

Adverse Reaction: All noxious and unintended responses to study drug at any dose should be considered to be adverse reactions. “Responses to study drug” means that there is a causal relationship between the study drug and the responses. “Suspected adverse reaction” implies a lesser degree of certainty about causality than “adverse reaction.”

Unexpected Adverse Reaction: An unexpected adverse reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For the study drug, the reference safety information is included in the current version of the Investigator’s Brochure. The reference safety information will be reviewed yearly, and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

6.16.2. Assessing Severity of Adverse Events

The assessment of severity must be provided by the Investigator and based on the Investigator’s clinical judgment. Maximum severity should be assigned to one of the following categories:

- Mild: An AE that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An AE that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An AE that prevents normal everyday activities.

An AE that is assessed as severe should not be confused with a serious AE (SAE). Refer to Section 6.17 for the definition of an SAE.

6.16.3. Assessing Relationship to Study Drug

The Investigator will categorize each AE as to its potential relationship to study drug: **unrelated**, **unlikely related**, **possibly related**, **probably related** and **definitely related**. Items to be considered when assessing the relationship of an AE to the study drug are as follows:

- Temporal relationship of the onset of the event to the initiation of the study drug
- The course of the event, considering especially the effect of discontinuation of study drug or reintroduction of study drug, as applicable
- Whether the event is known to be associated with the study drug or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study-drug-related factors that are known to be associated with the occurrence of the event

The relationship categories of unrelated and unlikely related will be summarized for reporting purposes as **Not Related**. For Not Related events, the time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship with study drug, and another cause of the AE (concomitant drugs, therapies, complications, etc.) is suspected.

The relationship categories of possibly, probably and definitely related will be summarized for reporting purposes as **Related**. Only AEs thought to be caused by the study drug should be classified as "related to study drug." For Related events, the time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship, and no other cause (concomitant drugs, therapies, complications, etc.) can be identified. The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

6.17. Serious Adverse Events

6.17.1. Definition of Serious Adverse Event

A serious adverse event (SAE) or reaction is any untoward medical occurrence that:

- Results in death
- Is life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which, in view of either the Investigator or Sponsor, the subject was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires in-patient hospitalization or prolongation of an existing hospitalization

  Notes:

Any hospital admission with at least one overnight stay will be considered an in-patient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness.

The following hospitalizations are not considered to be SAEs because there is no "AE" (i.e., no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite/hospice care
- Hospitalization planned prior to informed consent (where the condition requiring the hospitalization has not changed post study drug administration)

- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect, or
- Is determined to be an important medical event (at the discretion of the Investigator)
- Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in subject hospitalization, or the development of drug dependency or drug abuse.

6.17.2. Reporting SAEs – Procedure for Investigators

Initial Reports

SAEs, regardless of causality assessment, must be collected beginning from the time the subject signs the ICF until the end of the Follow-up period or 7 days after the last study procedure, whichever is longer. All SAEs must be reported to the CCI [redacted] **within 24 hours** of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned seriousness criteria).

To report the SAE, complete the SAE Report Form and submit to CCI [redacted]

After study completion, any SAE judged by the Investigator to be related to the study drug should be reported to the Sponsor regardless of the length of time that has passed since study completion.

It is very important that the SAE Form be filled out as completely as possible at the time of the initial report, including, the Investigator's assessment of causality. The minimum information

needed for making a preliminary SAE report is the protocol number, the subject ID, an AE term and the name of the person reporting the information to the Sponsor. Preliminary SAE reports should be followed as soon as possible by detailed descriptions including of hospital case reports, autopsy reports and other documents requested by the Sponsor (see Follow-up Reports, below).

Follow-up Reports

All AEs and SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Within 24 hours of receipt of Follow-up information, the Investigator must update the SAE Report Form and submit it along with any supporting documentation in case they have been requested by Sponsor/CCI (e.g., subject discharge summary or autopsy reports) to the CCI mentioned above.

The Investigator should notify the IRB of the occurrence of the SAE, in writing, in accordance with local requirements.

6.17.3. Pregnancy Reporting

If a subject becomes pregnant while in the treatment phase of the study, Investigators should immediately report it to CCI, discontinue study drug, and perform early termination study procedures. If a pregnancy occurs following study drug dosing, where the estimated date of conception occurred within 28 days of the last study drug dosing, this should also be reported. The subject should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify CCI by email/fax as mentioned in Section 6.17.2. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the fetus has a congenital anomaly, the Investigator should follow the procedures for reporting an SAE.

In addition, any pregnancy that occurs in a subject's partner, if the subject is active in the treatment phase or the estimated date of conception is within 75 days of the last study drug dosing, should be reported and followed until the pregnancy outcome is known. The investigator is required to obtain consent from subject's partner prior to reporting pregnancy information in the trial. Initial notification of any pregnancy (as defined above) should be made within 24 hours of awareness on the Pregnancy and Breastfeeding Exposure Reporting Form. **The contact information for reporting pregnancies is the same as for reporting SAEs** (Section 6.17.2).

6.17.4. Regulatory Reporting of Adverse Events

AEs will be reported to the regulatory authorities in compliance with local and regional law and established guidance by the Sponsor or by a third party acting on behalf of the Sponsor. The format of these reports will be dictated by the local and regional requirements.

6.18. Laboratory Tests

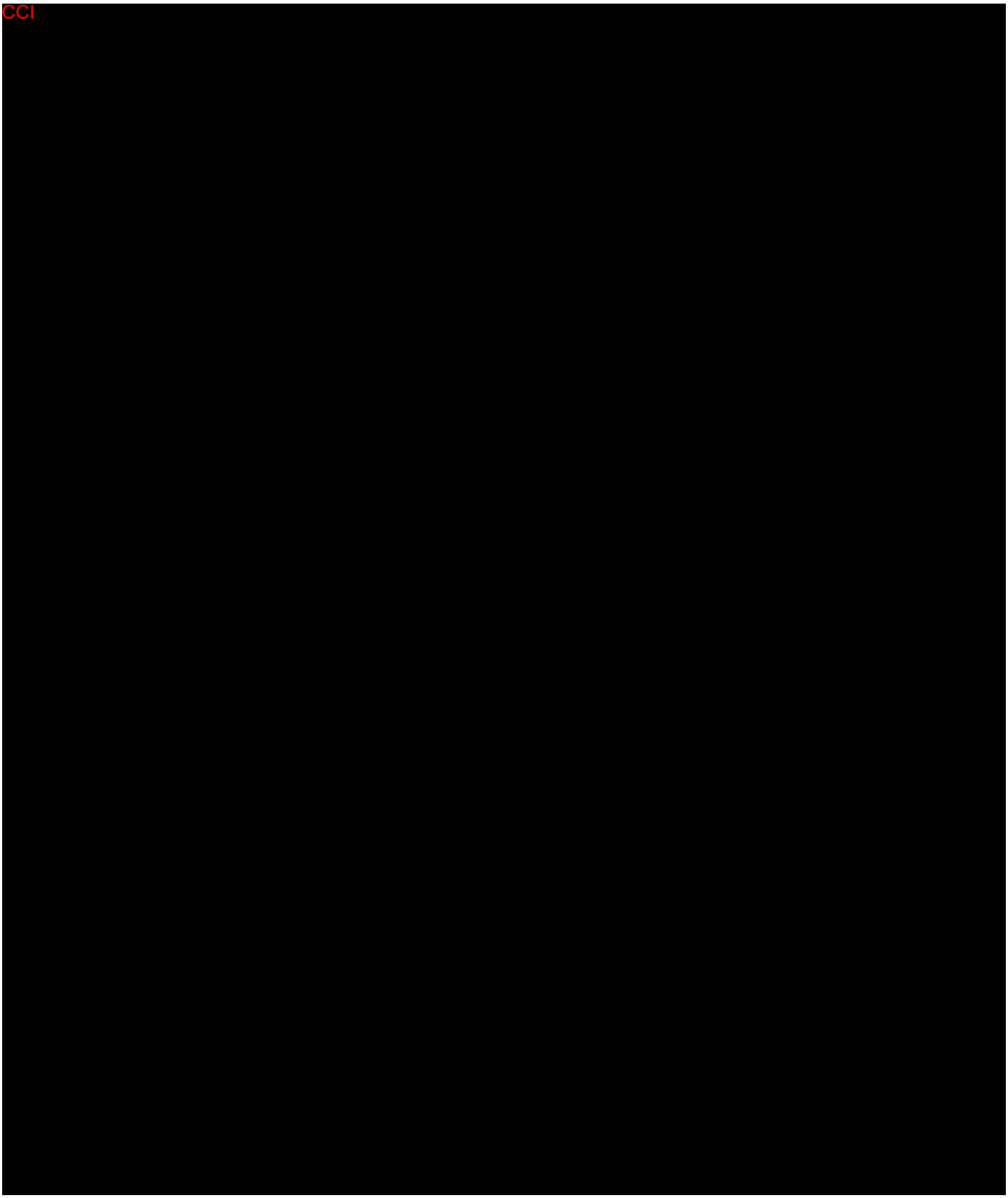
Blood and urine samples for assessments of clinical laboratory parameters and/or CCI will be obtained as shown in the study schedule in Table 1 Schedule of Activities. A fasting blood glucose will be required at Screening for all subjects. Diabetic subjects will be required to have fasting glucose at every study visit.

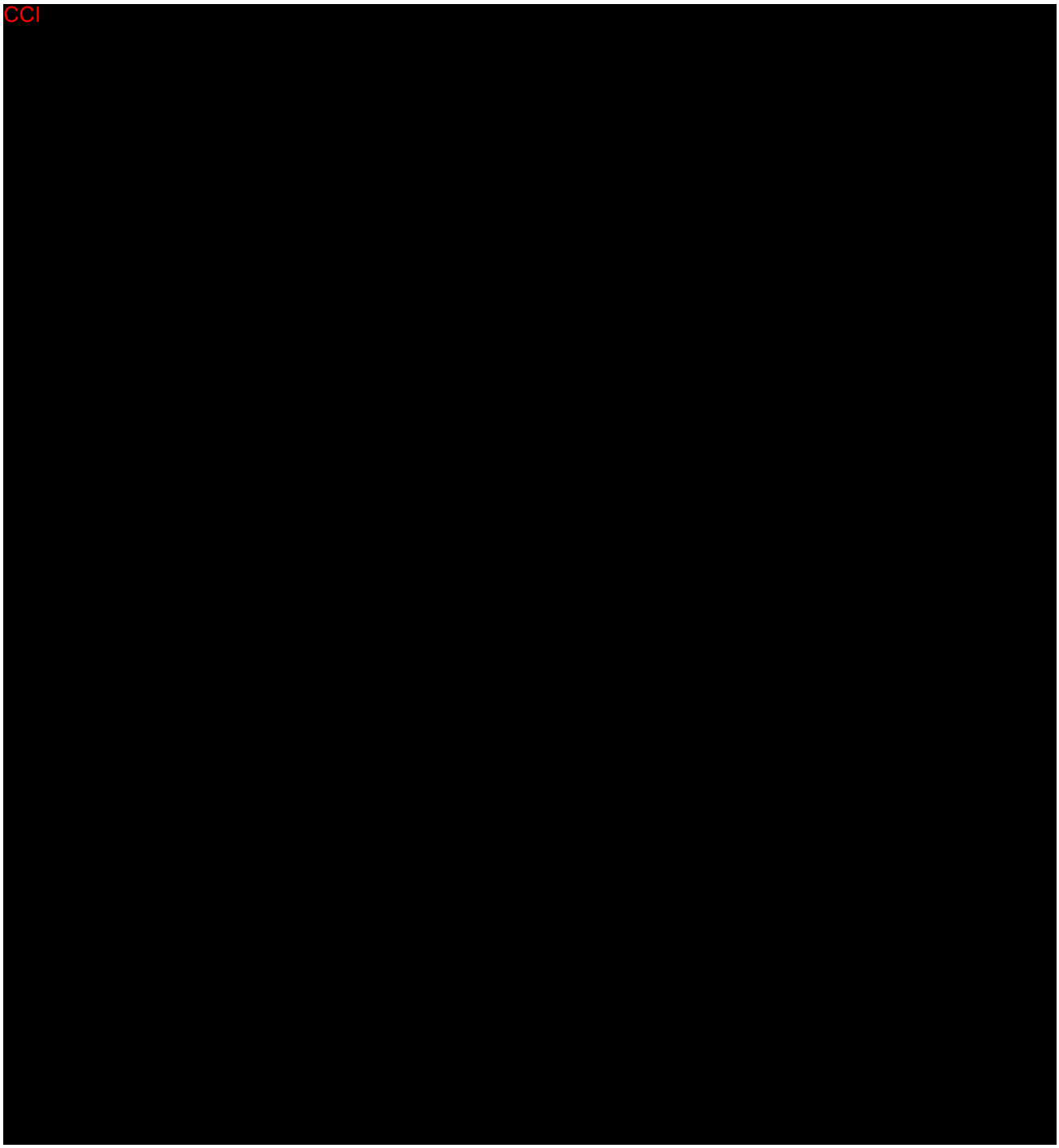
CCI



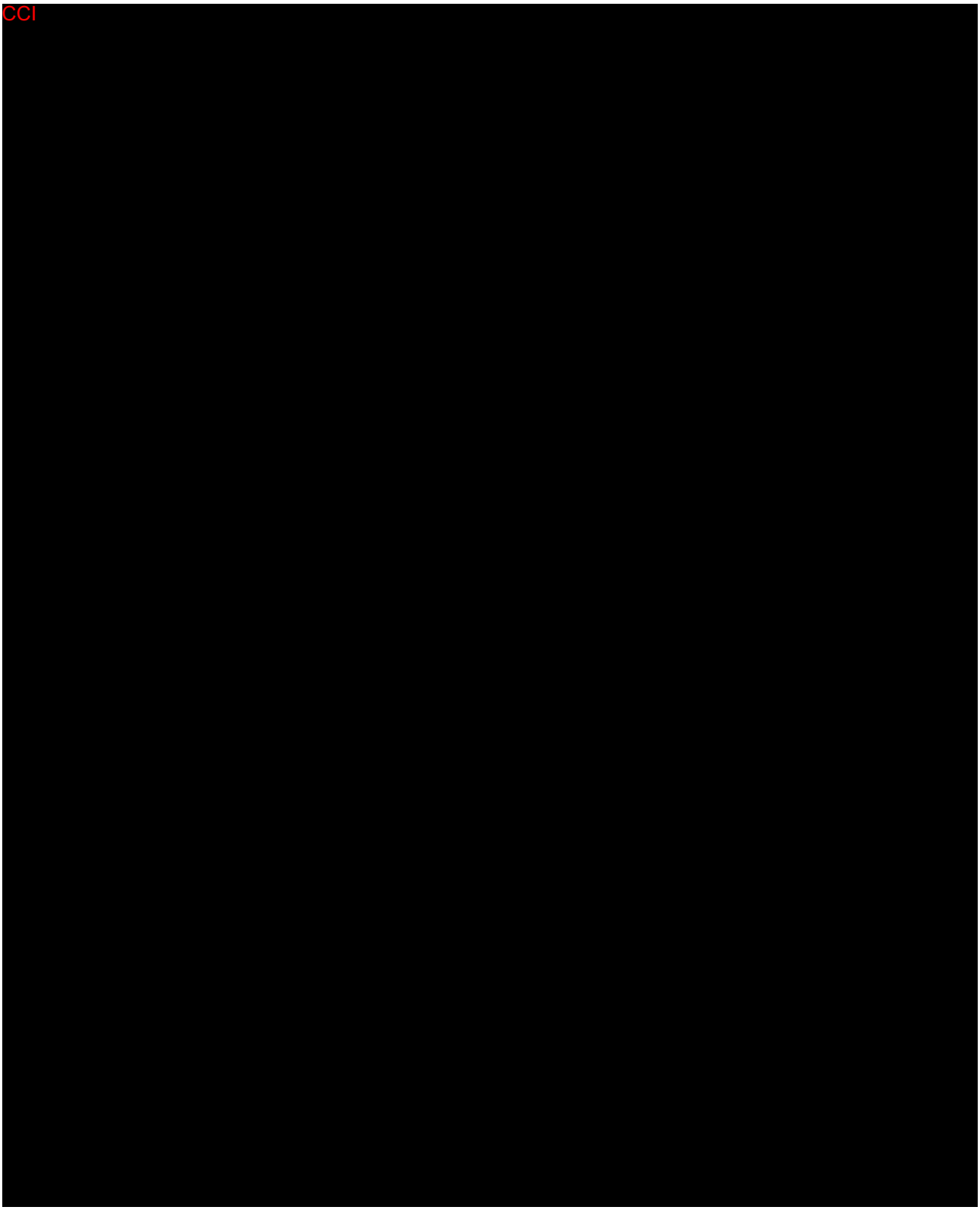

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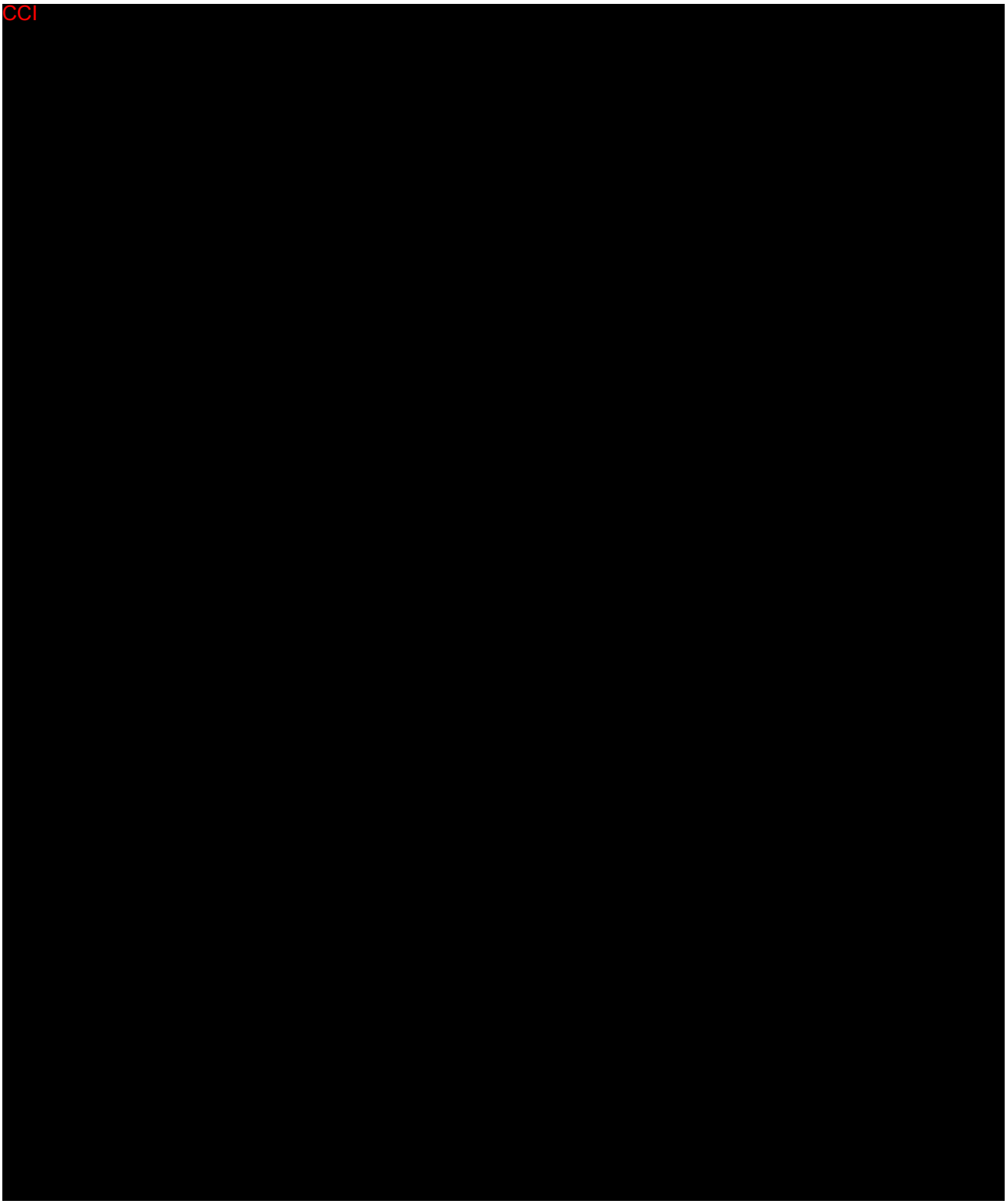



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6.20.1. Blood Sample Collection, Storage and Shipping

Sample collection, storage and shipment procedures for clinical laboratory samples are provided in the Central Laboratory Manual.

7. STUDY ACTIVITIES

Detailed schedules of study assessments are found in Table 1 Schedule of Activities.

When multiple assessments are scheduled for the same time, the order (as applicable) should be vital signs, ECG, CCI , and finally other blood samples, with the CCI being obtained as close as possible to the scheduled time.

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 IP 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 eCRF, with the reason for missing data being attributed to COVID-19.

If a subject misses a dose of study drug, he/she 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.

7.1. Study Activities

7.1.1. Screening Visit (Days -28 to Day -14)

The Screening visit will be conducted within 14 - 28 days prior to randomization. The date of screening is considered to be the date that the first study-related screening assessment is performed. During Screening, appropriate study site personnel will:

- Obtain written informed consent from the subject prior to any study procedures being performed
- Review all assessable inclusion and exclusion criteria
- Assign a study-specific subject ID and contact IRT to register the Screening Visit.
  - Collect urine sample for urinalysis and cotinine
- If female, of childbearing potential, collect serum pregnancy test
- Obtain medical and surgical history and demographic data, including smoking and child-bearing potential
- Review prior/concomitant medications
- Obtain vital signs, height and weight
- Perform a 12-lead ECG/QT evaluation
- Perform a complete physical examination
- Review adverse events

- Complete the efficacy assessments: CAS, CCI including proptosis, CCI and motility restriction, and ophthalmological exam. The CAS must be ≥ 4 for enrollment and randomization.
- Confirm that the subject has been fasting for at least 8 hours
- Obtain fasting glucose and total cholesterol and triglyceride
- Collect HbA1C blood sample
- Collect blood samples for hematology, chemistry, thyroid function tests, and viral screen (HBsAg, HCV, HIV)

For all subjects enrolled in the study, the source documentation record will be transcribed onto the eCRF. A limited number of eCRFs will be completed for subjects who screen fail. See eCRF Completion Guidelines for more detail.

7.1.2. Baseline Visit (Day 1) (visit window +/- 3 days)

Subjects will be assessed for eligibility prior to randomization. At the baseline visit, the appropriate study site personnel will:

- Collect urine sample for urinalysis
- Collect urine pregnancy test
- Review all assessable inclusion and exclusion criteria
- Obtain vital signs and weight
- Perform a 12-lead ECG/QT evaluation (pre-dose and hours 2, 3, and 4 post-dose). Subjects will remain at the clinic (within clinic/hospital grounds) for ECGs at Day 1 pre-dose and hours 2, 3, and 4 post-dose with the ECG leads attached at the pre-dose timepoint and kept in place until the 4-hour timepoint.
- Perform a complete physical examination including Pretibial Myxedema exam
- Record adverse events and concomitant medications
- Complete the efficacy assessments: CAS, CCI including proptosis, CCI and motility restriction, GO-QoL and ophthalmological exam. Subjects whose CAS score decreases 2 or more points from Screening to Baseline are not eligible for randomization. The CAS must be ≥ 4 for enrollment and randomization.
- Obtain fasting blood glucose
- Collect blood samples for hematology, chemistry, and Thyroid Function tests
- If subject continues to be eligible, randomize subject via IRT
- Dispense study medication and instruct the subject to self-administer study drug orally twice per day (first dose to be taken in the clinic, after CCI are drawn)
- CCI

CCI [redacted]

- Schedule the subject's next visit for morning clinic hours and remind them not to take their morning dose

7.1.3. Treatment Period Week 3 (visit window +/- 3 days)

- Collect urine sample for urinalysis
- Collect urine pregnancy test (for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug)
- Obtain vital signs and weight
- Perform a 12-lead ECG/QT evaluation (pre-dose, hours 2, 3, and 4 post-dose). Subjects will remain at the clinic (within clinic/hospital grounds) for ECGs at Week 3, pre-dose and hours 2, 3, and 4 post-dose with the ECG leads attached at the pre-dose timepoint and kept in place until the 4-hour timepoint.
- Record adverse events and concomitant medications
- Obtain blood glucose (fasting for diabetic subjects only)
- Collect blood samples for hematology and chemistry.

CCI [redacted]

- Dispense study medication and instruct subject to take morning dose
- Schedule the subject's next visit for morning clinic hours and remind them not to take their morning dose

7.1.4. Treatment Period Week 6 (visit window +/- 3 days)

- Collect urine sample for urinalysis

- Collect urine for pregnancy test (for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug)
- Obtain vital signs and weight
- Perform a 12-lead ECG/QT evaluation
- Perform a complete physical examination
- Record adverse events and concomitant medications
- Obtain blood glucose (fasting for diabetic subjects only)



- Collect blood samples for hematology, chemistry, and Thyroid Function tests.
- Complete the efficacy assessments: CAS, CCI including proptosis, CCI and motility restriction, GO-QoL and ophthalmological exam.
- Dispense study medication and instruct subject to take morning dose
- Perform Drug reconciliation

7.1.5. Treatment Period Week 9 (visit window +/- 3 days)

Collect urine sample for urinalysis

- Collect urine for pregnancy test (for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug)
- Obtain vital signs and weight
- Perform a 12-lead ECG/QT evaluation
- Record adverse events and concomitant medications
- Obtain blood glucose (fasting for diabetic subjects only)
- Collect blood samples for hematology and chemistry.
- Dispense study medication
- Drug reconciliation

7.1.6. Treatment Period Week 12 (visit window +/- 3 days)

- Collect urine sample for urinalysis

- Collect urine for pregnancy test (for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug)
- Obtain vital signs and weight
- Perform a 12-lead ECG/QT evaluation
- Perform a complete physical examination
- Record adverse events and concomitant medications

- Complete the efficacy assessments: CAS, CCI including proptosis, CCI and motility restriction, GO-QoL and ophthalmological exam.
- Obtain blood glucose (fasting for diabetic subjects only)
- Collect blood samples for hematology, HbA1C, chemistry, and Thyroid Function tests.
- Dispense study medication
- Drug reconciliation
- Schedule the subject's next visit for morning clinic hours and remind them not to take their morning dose

7.1.7. Treatment Period Week 15 (visit window +/- 3 days)

- Collect urine for pregnancy test (for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug)
- Obtain vital signs, and weight
- Perform a 12-lead ECG/QT evaluation
- Record adverse events and concomitant medications
- Obtain blood glucose (fasting for diabetic subjects only)
- Collect blood samples for hematology

CCI

- Dispense study medication and instruct subject to take morning dose
- Drug reconciliation

7.1.8. Treatment Period Week 18 (visit window +/- 3 days)

- Collect urine sample for urinalysis

- Collect urine for pregnancy test (for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug)
- Obtain vital signs and weight
- Perform a 12-lead ECG/QT evaluation
- Perform a complete physical examination
- Record adverse events and concomitant medications

- Complete the efficacy assessments: CAS, CCI including proptosis, CCI and motility restriction, and ophthalmological exam.
- Obtain blood glucose (fasting for diabetic subjects only)
- Collect blood samples for hematology, chemistry, and Thyroid Function tests.
- Dispense study medication
- Drug reconciliation

7.1.9. Treatment Period Week 21 (visit window +/- 3 days)

- Collect urine for pregnancy test (for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug)
- Obtain vital signs and weight
- Perform a 12-lead ECG/QT evaluation
- Record adverse events and concomitant medications
- Obtain blood glucose (fasting for diabetic subjects only)
- Collect blood samples for hematology.
- Dispense study medication
- Drug reconciliation
- Schedule the subject's next visit for morning clinic hours. The last dose of study medication is taken the evening prior to the Week 24 visit.

7.1.10. Treatment Period Week 24/End of Treatment (EOT)

Week 24 is the end (last visit) of the Double-mask Period; no study drug is dispensed at this visit. The visit window for this visit is +/- 3 days.

At the end of the Double-mask Treatment Period (Week 24), subjects who are proptosis non-responders (primary study eye has < 2 mm decrease in proptosis) will be eligible to enter an extension study (VGN-TED-302) (See Section 2.3 for details).

Subjects on placebo during the Double-mask Treatment Period will be randomized to receive either 75 mg BID or 150 mg BID linsitinib. Subjects randomized to linsitinib during the Double-mask Treatment Period will continue on the linsitinib dose they were randomized to during the Double-mask Treatment Period. All subjects will be masked to the study medication dose (See Section 2.3).

At Week 24, proptosis responders, as well as 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.

Collect urine sample for urinalysis

- Collect urine pregnancy test
- Obtain vital signs and weight
- Perform a 12-lead ECG/QT evaluation
- Perform a complete physical examination including Pretibial Myxedema exam
- Record adverse events and concomitant medications
- Complete the efficacy assessments: CAS, CCI including proptosis, CCI and motility restriction, GO-QoL and ophthalmological exam
- Obtain blood glucose (fasting for diabetic subjects only)
- Collect blood samples for hematology, chemistry, HbA1C, and Thyroid Function tests.

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- Drug reconciliation, including a complete disposition of all previously dispensed study medication bottles

7.1.11. Follow-up Period Week 28 (visit window +/- 7 days)

During the Follow-up period, the continued safety of the subjects after discontinuation of study drug will be assessed.

- Obtain vital signs and weight
- Collect urine pregnancy test
- Perform a 12-lead ECG/QT evaluation
- Record adverse events and concomitant medications
- Complete the efficacy assessments: CAS, CCI including proptosis, CCI and motility restriction, GO-QoL and ophthalmological exam

7.1.12. Follow-up Period Week 36 (visit window +/- 7 days)

- Collect urine sample for urinalysis
- Obtain vital signs and weight
- Perform a 12-lead ECG/QT evaluation
- Record adverse events and concomitant medications
- Complete the efficacy assessments: CAS, CCI including proptosis, CCI and motility restriction, and ophthalmological exam

- Obtain blood glucose (fasting for diabetic subjects only)
- Collect blood samples for hematology, chemistry, HbA1C, and Thyroid Function tests.

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7.1.13. Follow-up Period Week 48 (visit window +/- 7 days)

- Obtain vital signs and weight
- Perform a 12-lead ECG/QT evaluation
- Perform a complete physical examination
- Record adverse events and concomitant medications
- Complete the efficacy assessments: CAS, CCI [redacted] including proptosis, CCI [redacted] and motility restriction, GO-QoL and ophthalmological exam

7.1.14. Follow-up Period Week 60 (visit window +/- 7 days)

- Record adverse events and concomitant medications
- Obtain vital signs and weight
- Perform a 12-lead ECG/QT evaluation
- Complete the efficacy assessments: CAS, CCI [redacted] including proptosis, CCI [redacted] and motility restriction

7.1.15. Follow-up Period Week 72 / Early Termination (ET) (visit window +/- 7 days)

- Collect urine sample for urinalysis
- Obtain blood glucose (fasting for diabetic subjects only)
- Obtain vital signs and weight
- Record adverse events and concomitant medications
- Perform a 12-lead ECG/QT evaluation
- Perform a complete physical examination including Pretibial Myxedema exam
- Complete the efficacy assessments: CAS, CCI [redacted] including proptosis, CCI [redacted] and motility restriction, GO-QoL and ophthalmological exam
- Collect blood samples for hematology, chemistry, HbA1C, and Thyroid Function tests.
- Confirm details on best method and form of subject contact during the extended Follow-up period.

7.1.16. Extended Follow-up Period, Week 96 and Week 120/End of Study (EOS)

Subjects who complete the Week 72 Visit will be contacted 6 and 12 months later via phone or email by research staff (Week 96 and Week 120, respectively). Research Staff will enquire if any treatment for TED has been received since last study contact. If yes, subject will be questioned regarding type of treatment and outcome/response. Concomitant medications and adverse events will also be recorded.

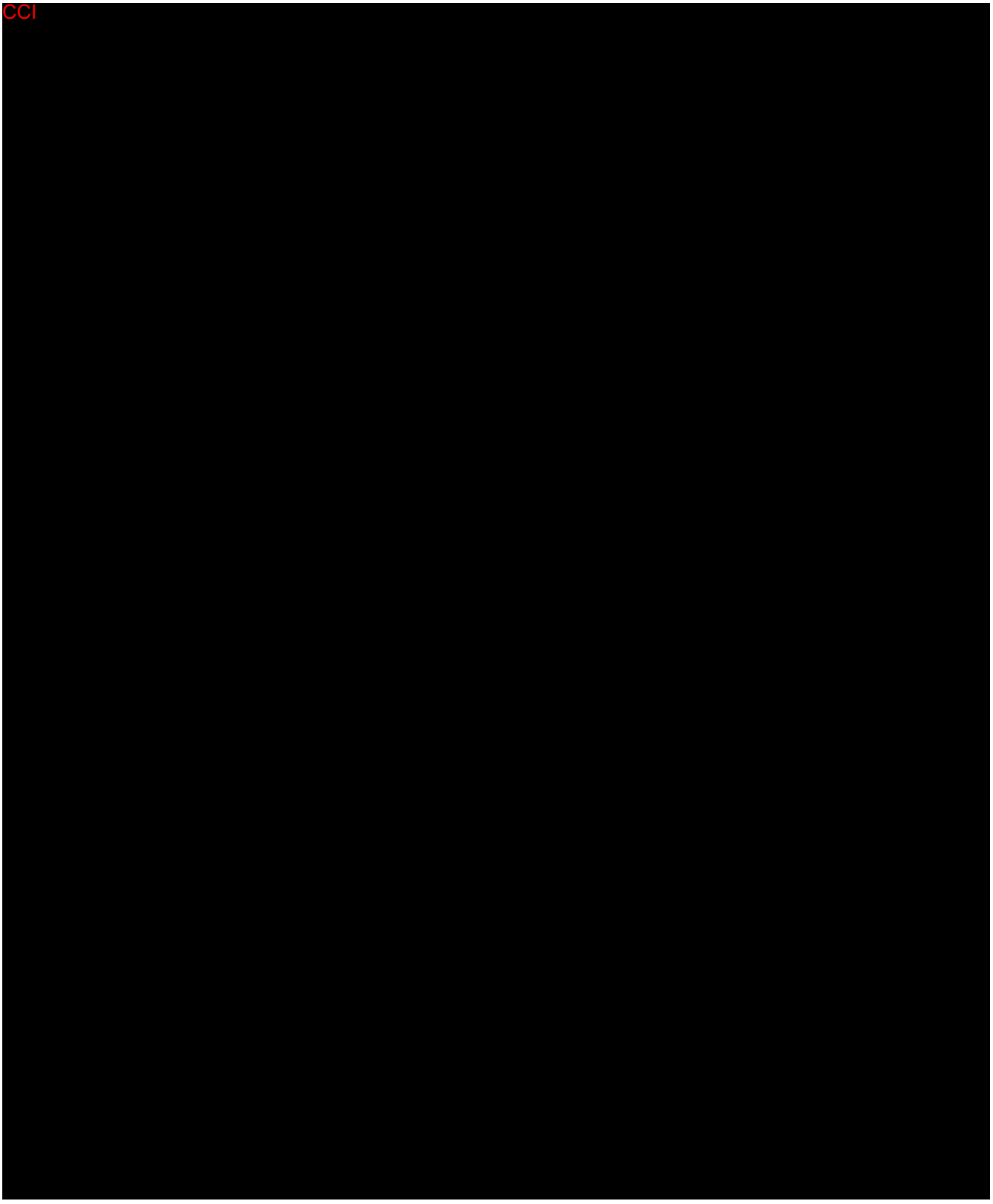
The end of the study is defined as the date of the last subject contact at Week 120.

8. QUALITY CONTROL AND ASSURANCE

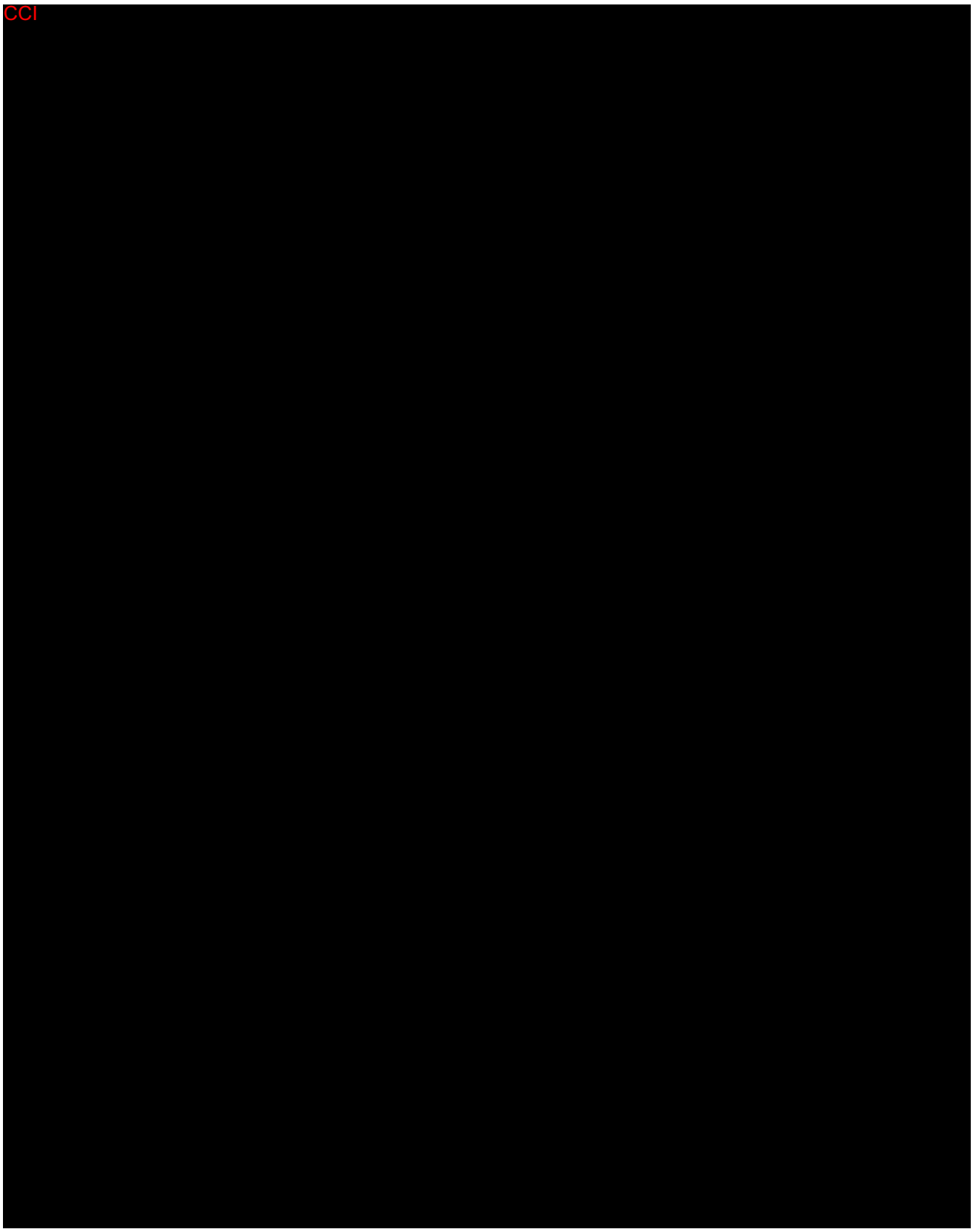
Before any subjects can be consented at an investigational site and prior to the conduct of any protocol-specific procedures, formal training of investigational site personnel will be conducted. The Investigator and all relevant investigational site staff are to be trained on all aspects of the study for which they are responsible. Site personnel may be trained at a formal initiation visit, at an Investigator's Meeting, or by another means as necessary. Monitoring and auditing procedures will be conducted in compliance with the International Council for Harmonization (ICH) Guidelines for Good Clinical Practice (GCP). Onsite and remote verification of the eCRFs for completeness and clarity, crosschecking with source documents and clarification of administrative matters will be performed on a regular basis. Monitoring visits will occur at regular intervals as noted in the monitoring plan. Through frequent communications with the investigational site, the clinical research associate (CRA) will ensure that the investigation is conducted according to protocol design and all applicable regulatory requirements. Additional details on the monitoring of this study are provided in Section 10.5. During the course of the study, investigational sites, the study database and all associated study documentation may be subject to quality assurance audits by the Sponsor, or their appointed representatives, on a planned or as-needed basis. In addition, representatives of associated regulatory bodies may conduct inspections at their discretion. The Investigator is responsible for ensuring direct access to all protocol-specific materials for the purpose of these activities.

9. STATISTICS

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9.5. Efficacy Analyses

The primary analyses will be conducted in the Intent-to-Treat (ITT) population according to the treatment to which they were randomized.

9.5.1. 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. 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 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 other visits of the treatment period (Week 3 to Week 21) except for Week 24, but also for the visits of the follow-up period (Week 28 to Week 72) on the ITT and PP populations.

9.5.2. Secondary Efficacy Estimands and Analyses

9.5.2.1. 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. 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 the visits of the follow-up period (Week 28 to Week 72) on the ITT and PP populations. 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.

9.5.2.2. 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 for the primary efficacy estimand will be applied for this secondary efficacy estimand.

9.5.2.3. 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 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.

9.5.2.4. 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'.

9.6. Safety Analyses

The safety population will be used for all summaries of safety data. Only observed case data will be used. The summarization of AEs will include treatment-emergent AEs (TEAEs; defined as AEs that begin or worsen after the first dose of study drug). TEAEs and treatment-emergent SAEs (TESAEs) will be summarized by system organ class (SOC), preferred term (PT), severity, and relationship to study drug for each treatment group. Deaths and discontinuations due to AEs will be listed. Clinical safety laboratory results, vital signs, physical examination findings, and ECG parameters will be summarized by observed value and by change from baseline, where appropriate, by time point. Counts will be used for categorical parameters.

9.7. Interim Analysis

There is no planned interim analysis for this study.

10. ADMINISTRATIVE CONSIDERATIONS

10.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Prior to initiation of the study at each investigational site, the protocol, Investigator Brochure (IB) the ICF(s), the subject information sheet(s), details of the subject recruitment procedures and any other relevant study documentation will be submitted to the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) for review and approval. A letter indicating approval of the Investigator and study site must be submitted to the study Sponsor. All reviews and approvals by the IRB or IEC will be in accordance with Title 21 of the Code of Federal Regulations (CFR), Part 56 and the European Union Clinical Trials Directive (2001/20/EC), and applicable laws and regulations. Initial IRB approval and all materials approved by the IRB/IEC for this study including the ICF and recruitment materials must be maintained by the Investigator and made available for inspection.

The Investigator will promptly report any new information that may adversely affect the safety of subjects or the conduct of the study to the appropriate regulatory authorities. Similarly, the Investigator will submit written summaries of the study status annually, or more frequently if requested. Upon completion of the study, the Investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

10.2. Ethical Conduct of the Study

The guidelines of the World Medical Association Declaration of Helsinki in its revised edition (52nd General Assembly, Edinburgh, Scotland, October 2000), the guidelines of ICH GCP (Committee for Proprietary Medicinal Products (CPMP)/ICH/135/195), and the European Union Clinical Trials Directive (2001/20/EC) as well as the demands of national drug and data protection laws and other applicable regulatory requirements, will be strictly followed.

10.3. Subject Information and Consent

The Investigator is responsible for ensuring that subjects do not undergo any study-related examination or activity before giving informed consent. The subject must give written consent after the receipt of detailed information regarding the study. The verbal explanation will cover all the elements specified in the written information provided to the subject. If the written informed consent is provided by the legal guardian because the subject is unable to do so, a written or verbal assent from the subject must also be obtained.

The Investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and must be provided with more information if requested. At the end of the interview, the subject may be given time to reflect and can request more time if needed. The subject and/or legal guardian (if applicable) will be required to sign and date the ICF. After completion, ICFs will be kept and archived by the Investigator in the Investigator study file.

It should be emphasized to the subject that he or she is at liberty to either discontinue study drug and/or withdraw consent to participate at any time, without penalty or loss of benefits to which he or she is otherwise entitled. Subjects who refuse to give or withdraw written informed consent may not be included or continued in this study, but this will not affect their subsequent care.

The subject shall be provided with a contact point where he or she may obtain further information prior to or during the course of their study participation.

Please refer to Title 21 of the CFR, Part 50 – Protection of Human Subjects, and the European Union Clinical Trials Directive, Article 6, for specific details on these regulations.

10.4. Subject Confidentiality and Data Protection

Personal and sensitive data will be treated as confidential. The results of the study will be made available for review by authorized representatives of the Sponsor and/or submitted to the IRB/IEC and regulatory authorities. All subject personal information will be held in confidence and in accordance with data protection laws.

Prior to any Screening procedures being performed; the subject's consent is required for the data to be used for these purposes and to gain direct access to their medical records for data verification purposes. The subject must be assured that their identity will be protected. To facilitate this, a unique identification number will be assigned, and it will be used when reporting study-related data.

Additionally, in the US, the Health Insurance Portability and Accountability Act of 1996 ("HIPAA") requires that all subjects grant permission to use their personal health information. Therefore, in addition to the protocol specific ICF, each subject located in the United States (US) will be asked to provide authorization to use his/her personal health information by signing a separate HIPAA Authorization Form.

10.5. Study Monitoring

It is understood that the Sponsor or its designee (e.g., the CRA) will contact and visit the Investigator regularly for monitoring purposes. The CRA will be allowed, on request, to inspect the various records of the study (i.e., eCRFs, source documents, and any other pertinent data), provided that subject confidentiality is maintained in accordance with local requirements. It will be the CRA's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify adherence to the protocol and to ensure the completeness, consistency and accuracy of the data entered. The CRA must have access to all subject records needed to verify the entries on the eCRF. The Investigator agrees to cooperate with the CRA to ensure that problems detected during these monitoring visits are resolved. In the unlikely event of site closure or restricted access due to COVID-19, sites should allow for remote review of medical records and other documents normally reviewed on site. In some instances, requests for certified copies uploaded to a secure portal may be requested. Sites should document subjects who are impacted by a disruption in study participation due to COVID-19.

Before an investigational site can consent a subject into the study, a representative of the Sponsor will evaluate the investigational study site to assess the site including but not limited to:

- Determine the adequacy of the facilities including the site's ability to carry out the protocol
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence and the responsibilities of the Sponsor or its representatives. This will also be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following but not limited to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs and that investigational product accountability checks are being performed
- Perform source data verification (SDV). This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts). Remote SDV may be performed if needed and if permitted by the study site.
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the Sponsor or designee and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

10.6. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an Ethics Committee or an IRB may visit the site to perform audits or inspections, including source data verification. The Sponsor may perform Clinical Quality Assurance (CQA) audits from time to time at a random sample of clinical sites, or for cause as warranted. The purpose of a Sponsor CQA audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed and accurately reported according to the protocol, GCP guidelines of the ICH and any applicable regulatory requirements. These audits will be independent of routine monitoring by the CRA and initiated with prior written notification provided to the site.

The Investigator must contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

10.7. Case Report Forms and Study Records

This study will utilize an electronic data capture system for the management of clinical data. The data will be collected in electronic form (i.e., via an eCRF) to allow for data entry at the site from source documentation directly into the electronic database. Access to the electronic system will

be restricted and users will only be able to access the system via authorized individual accounts. Data will be reviewed for errors, completeness, and for clarification as needed. Sites will be contacted to provide such clarification until potential data issues are resolved. All changes to data in the database will be tracked and time stamped automatically, including updates to data entries, and resolution of data queries generated (by the CRA or data reviewer).

Training will be provided to all system users based on their individual access and use requirements initially and ongoing throughout the course of the study as needed. Documentation of training will be kept in the site regulatory file and in Sponsor's trial master file (TMF).

A comprehensive Data Management Plan will be written outlining the standard operating procedures, internal/external security safeguards, system and change controls and training procedures and will be filed in the Sponsor's TMF. A cumulative record will also be kept of the user and access privileges for all authorized users across the study.

The system and procedures for electronic database set-up, entry, review, access, security and auditing are designed in specific compliance with 21 CFR 11 and the Food and Drug Administration's (FDA) Part 11 Guidance for Industry supplement "Computerized Systems Used in Clinical Investigations" dated May 2007. Any additional electronic systems that may be used by vendors (e.g., CCI or clinical sites (e.g., electronic medical records used as source documents) should comply with these same regulatory standards.

Coding of medical history, adverse events, and concomitant medications will be done using the Medical Dictionary for Regulatory Authorities (MedDRA), and the World Health Organization Drug Dictionary (WHODrug).

As a final step in the data management process, a 100% quality control review will be performed on the queries associated with the agreed upon critical datapoints.

All unused study materials are to be returned or destroyed as instructed by the Sponsor after the study has been completed.

10.8. Data Safety Monitoring Board

A Data Safety Monitoring Board (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.

10.9. Protocol Deviations

Protocol deviations from inclusion/exclusion criteria, concomitant medication restrictions and from any other protocol requirements that could, at least hypothetically, result in significant risk to the subject, data integrity, and/or affect the outcome of the study will be collected. Additionally, nonadherence to the study procedures or schedule as defined by the protocol such

as a missed procedure or an out-of-window study visit will be documented as protocol deviations.

10.10. Access to Source Documentation

The Investigator must permit the authorized Sponsor, agents of the Sponsor and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held and to inspect and copy all records relating to an investigation including subject records. To ensure the accuracy of data submitted, it is mandatory that representatives of the Sponsor and of the regulatory agencies have direct access to source documents (e.g., subject medical records, charts, laboratory reports) for the purpose of quality assurance audits either by the Sponsor or its appointed representatives. Subject confidentiality will be protected at all times.

10.11. Data Generation and Analysis

Data processing and management will be performed by the Sponsor or its designee. Data will be promptly entered into the study database by the site and reviewed and issues resolved prior to database closure.

Personal and sensitive personal data will be treated as confidential. The results of the study will be made available for review by authorized representatives of the Sponsor and/or submitted to the IRB and regulatory authorities.

10.12. Retention of Records

Copies of all study documents should be retained by the Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product, in accordance with 21 CFR 312.62. These documents should be retained for a longer period, however, if required by regulatory requirements or by agreement with the Sponsor. The Investigator must inform the Sponsor and obtain agreement prior to study documents being moved or destroyed. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. The final database will be archived by the Sponsor according to regulatory requirements.

10.13. Financial Disclosure

Investigators and Sub investigators are required to provide full disclosure of any financial relationship to the Sponsor or its designee(s) prior to participation in any study-related activities. Additionally, Investigators and Sub investigators are required to promptly provide updated information to the Sponsor or its designee(s) regarding any relevant changes in financial interests that occur during the course of the study and for one year after completion of the study. For additional guidance, refer to 21 CFR 312.53(c) (4), 312.64(d), 812.43(c) (5), 812.110(d).

10.14. Premature Termination of the Study

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and the regulatory authority(s) of the termination or suspension and the

reason(s) for the termination or suspension. The IRB will also be promptly informed and provided with the reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

10.15. Clinical Study Report (CSR)

A CSR will be written for this study with a structure and content that will conform to the ICH guidance, "Structure and Content of Clinical Study Reports, ICH Topic E3, July 1996."

10.16. Subject Insurance and Indemnity

The Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects participating in this study. The terms of insurance will be kept in the Sponsor's regulatory files.

10.17. Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The IRB must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented.

The Investigator must not implement any deviation from or change to the protocol without discussion and agreement by the Sponsor in writing and prior review and documented approval/favorable opinion of the amendment from the relevant IRB, except where it is necessary to eliminate an immediate hazard to study subjects or where the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor or change of telephone number).

Protocol amendments will be submitted to the appropriate authority(s) as required by the applicable regulatory requirement(s).

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12. APPENDICES

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12.1. STUDY SCHEDULE OF ACTIVITIES

Schedule of Activities

Phase 2b Trial - Thyroid Eye Disease

Study Period	Screening	Baseline/ Randomization	Double-blind 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	W72/ET	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		
Opthalmologic exam[4]	X	X		X		X		X		X	X	X	X		X		
ECG/QT Evaluation[5]	X	X[6]	X[6]	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 (HIV, Hep B, Hep C)	X																
Randomization via IRT and First Dosing		X															
Dispense study drug		<----------								->[12]							
Drug Reconciliation			<----------							->[12]							
Clinical Activity Scale (CAS) [10]	X	X		X		X		X		X	X	X	X	X	X		
CCI																	
GO-QOL		X		X		X				X	X		X		X		
CCI																	
Adverse Events	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 (ET), End of Study (EOS), End of Treatment (EOT)

[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]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.

[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]ALT/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.

CCI [redacted]

[12]Arrows indicate drug dispensing and reconciliation. For more detailed information, please see the Pharmacy Manual.

12.2. Resource for Identifying Medications with a Potential Risk of QT Prolongation

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.

Please note that all medications in the following QT/TdP Risk Categories from crediblemeds.org are prohibited 14 days prior to Day 1 dosing through Week 72 of Follow-up Period.

Known Risk of TdP - These drugs prolong the QT interval **AND** are clearly associated with a known risk of TdP, even when taken as recommended.

Possible Risk of TdP - These drugs can cause QT prolongation **BUT** currently lack evidence for a risk of TdP when taken as recommended.

Conditional Risk of TdP - These drugs are associated with TdP **BUT** only under certain conditions of their use (e.g. excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) **OR** by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).

12.3. Graves' Ophthalmology Quality of Life Questionnaire

Graves' Ophthalmopathy Quality of Life Questionnaire (GO-QOL)

The following questions relate specifically to your Graves' eye disease.
When answering the questions, think about the past week.
Over the past week, to what extent has your ability to carry out the following activities been limited by having Graves' eye disease?
Place an X in the box that matches your answer. The boxes match the answers above. Place an X in one box for each question.

	Yes, severely limited	Yes, slightly limited	No, not at all limited
1. Riding a bike [never learned to ride a bike ☐]	☐	☐	☐
2. Driving a car [no driver's license ☐]	☐	☐	☐
3. Moving in and around the house	☐	☐	☐
4. Walking outside	☐	☐	☐
5. Reading	☐	☐	☐
6. Watching TV	☐	☐	☐
7. Hobby or leisure activity, specifically	☐	☐	☐

	Yes, seriously interfered	Yes, interfered somewhat	No, did not interfere at all
8. In the past week, did your Graves' eye disease interfere with you doing something you wanted to do?	☐	☐	☐

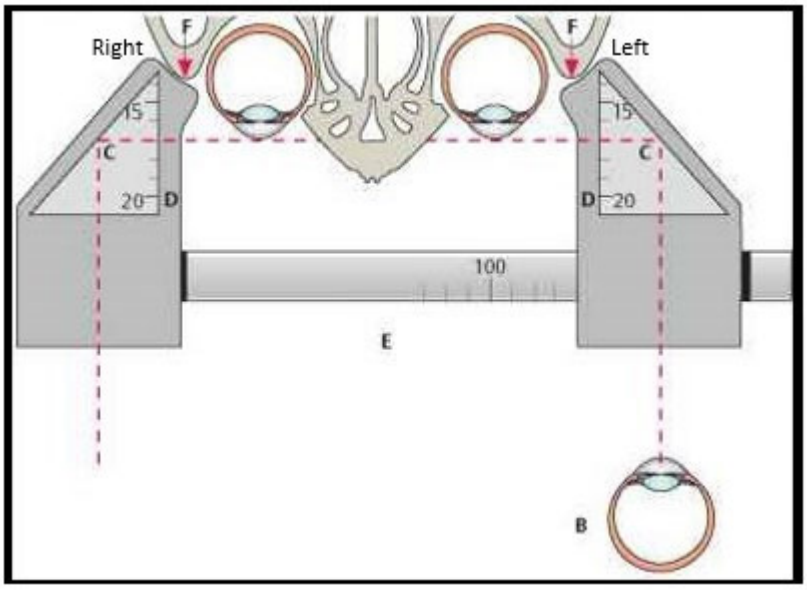
The following questions relate to your Graves' eye disease in general

	Yes, a lot	Yes, a bit	No, not at all
9. Do you think that your appearance has changed because of your Graves' eye disease?	☐	☐	☐
10. Do you feel that people stare at you when out in public because of your Graves' eye disease?	☐	☐	☐
11. Do you feel that people react negatively because of your Graves' eye disease?	☐	☐	☐
12. Do you feel that your Graves' eye disease affects your self-confidence?	☐	☐	☐
13. Do you feel that your Graves' eye disease affects your ability to make friends?	☐	☐	☐
14. Do you think you are socially isolated because of your Graves' eye disease?	☐	☐	☐
15. Do you feel that you are in photos less than you used to be, before you had Graves' eye disease?	☐	☐	☐
16. Do you make an effort to hide changes in your appearance that are a result of your Graves' eye disease?	☐	☐	☐

12.4. Proptosis (Exophthalmometry) Method

1. Use only the Hertel exophthalmometer provided by Study Sponsor
2. Sit at same level and opposite the study subject
3. Open device wider than needed
4. Place device on the lowest point of temporal zygomatic arch. At level of lateral canthus, position left arm of device (D) against subject's right lateral orbital rim (F). (Note: Firmly fit exophthalmometer arm as medially as possible outside the lateral canthus. Be careful to not distort the position of the globe.)
5. Firmly fit right arm medially into the same position on subject's left orbital rim (F). (Note. While uncomfortable, the firm fit will minimize slippage of device.) To obtain reproducible results, maintain a constant base setting in mm (E) every time the exophthalmometer is applied to a given subject.
6. Subject is told to focus their left eye on investigator's right eye (B). Investigator blocks the subject's right visual field with left thumb.
7. Align cone (vertical mark) of device with the marked position on ruler. This is best achieved by the examiner moving their eye horizontally to align the two integral graduations in the mirror (C) in order to avoid parallactic measurement errors. Along horizontal plane, rotate device to view apex of cornea (extraorbital prominence of the anterior surface of the cornea) in mirror. The position of the corneal apex on the scale (red dotted line) is the Hertel value.

8. Hold device in place and position yourself to use your left eye to record the subject's right eye. Investigator blocks the subject's left visual field with right thumb while subject focuses their right eye on investigator's left eye. Once again, rotate device along horizontal plane to measure the apex of cornea.


Right
F
F
Left
15
C
20
D
D
20
15
C
100
E
B