CLINICAL STUDY PROTOCOL

Protocol Title:

A Phase 2, Proof-of-Concept, Randomized, Double-Masked, Placebo-Controlled Study to Determine the Efficacy and Safety of LASN01 in Patients with Thyroid Eye Disease

Protocol Number:	LASN01-CL-2201
Version Number:	7.0, United States Amendment Only
Compound:	LASN01
Study Phase:	Phase 2
IND Number:	167553
EU CT Number:	2023-508161-32-00
Sponsor Name:	Lassen Therapeutics 1, Inc. (Lassen Therapeutics)
Legal Registered Address:	5510 Morehouse Dr., Suite 100, San Diego, CA 92121 Telephone: +1 858-251-7528
Sponsor Medical Representative:	[redacted]
Version Date:	15NOV2024

INVESTIGATOR SIGNATURE PAGE

I have read and understand protocol LASN01-CL-2201 (dated 15NOV2024). I agree to the following:

1. To conduct the trial in compliance with Good Clinical Practice, with applicable regulatory requirement(s), with the protocol agreed to by the Sponsor and given approval/favorable opinion by the concerned regulatory authority and/or ethics committee
2. To comply with procedures for data recording and reporting
3. To permit monitoring, auditing, and inspection by the Sponsor, its designated representatives, and regulatory authorities
4. To retain the essential documents in the Investigator/institution files until the Sponsor informs the Investigator or institution that these documents are no longer needed

INVESTIGATOR SIGNATURE:

_____ _____
[Investigator Signature] Date

_____
[Investigator Name]

_____
[Site Name]

SPONSOR APPROVAL PAGE

Protocol: LASN01-CL-2201

A Phase 2, Proof-of-Concept, Randomized, Double-Masked, Placebo-controlled Study to Determine the Efficacy and Safety of LASN01 in Patients with Thyroid Eye Disease

Protocol Version 7.0-US: 15NOV2024

[redacted]

11/15/2024

Signature Date

[redacted]

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LIST OF ACRONYMS, ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
$AUC_{0-\infty}$	area under the time-concentration curve from start of infusion extrapolated to time infinity
AUC_{0-15d}	area under the time-concentration curve from start of infusion to 15 days after start of the infusion
AUC_{0-28d}	area under the time-concentration curve from start of infusion to 28 days after start of the infusion
AUC_{0-last}	area under the time-concentration curve from start of infusion to last measurable serum concentration
AUC_{85-99d}	area under the time-concentration curve from Day 85 to Day 99 (ie, 0 to 14 days after fourth dose)
BMI	body mass index
CAS	clinical activity score
CL	total body clearance
C_{max}	maximum serum concentration
CRO	clinical research organization
CSR	clinical study report
CT	computed tomography
CV%	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End of Study
ERK	extracellular signal-regulated kinase 1
EOT	End of Treatment
ETDRS	Early Treatment of Diabetic Retinopathy Study
EUGOGO	European Group on Graves' Orbitopathy
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FU	follow-up
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
gp130	glycoprotein 130
HA	hyaluronic acid
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IGF-1	insulin-like growth factor 1
IGF-1R	insulin-like growth factor 1 receptor
IgG4κ	immunoglobulin G4 kappa
IL	interleukin
IL-11R	interleukin-11 receptor

Abbreviation	Definition
IND	Investigational New Drug
IP	investigational product
IPF	idiopathic pulmonary fibrosis
IRT	interactive response technology
IV	Intravenous(ly)
λz	elimination rate constant
MAD	multiple ascending dose
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Mode Repeated Measures
MRD	margin reflex distance
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NOAEL	no-observed-adverse-effect level
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PF-ILD	progressive fibrosing interstitial lung diseases
PI	Principal Investigator
PK	pharmacokinetic(s)
Q2W	every 2 weeks
Q4W	every 4 weeks
QTcF	QT interval, corrected for heart rate according to Fridericia's formula
SAD	single ascending dose
SAE	serious adverse event
SAER	serious adverse event report
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome associated coronavirus 2
SOC	standard-of-care
SOP	standard operating procedure
SRC	Safety Review Committee
STAT3	signal transducer and activator of transcription-3
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TED	thyroid eye disease
TGFβ	transforming growth factor beta
TIMP1	tissue inhibitor of metalloproteinase 1
T_{max}	time to maximum serum concentration
TRAE	treatment-related adverse event
TSH	Thyroid stimulating hormone
T3	Triiodothyronine
T4	Thyroxine
UA	urinalysis
V_{ss}	volume of distribution at steady state

Abbreviation	Definition
V_z	volume of distribution
WFI	Water for Injection
WOCBP	women of child-bearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2, Proof-of-Concept, Randomized, Double-Masked, Placebo-Controlled Study to Determine the Efficacy and Safety of LASN01 in Patients with Thyroid Eye Disease

Rationale:

LASN01 is a first-in-class, fully human, IgG4κ monoclonal antibody directed against human IL-11R that has demonstrated compelling antifibrotic activity in nonclinical studies and is in development for the treatment of patients with TED.

A first-in-human Phase 1/2a (LASN01-CL-1101) randomized, double-blind, placebo-controlled, SAD, and MAD clinical study is ongoing in Australia to determine the safety, tolerability, preliminary efficacy, immunogenicity, and PK properties of LASN01 in healthy volunteers and in patients with pulmonary fibrosis and TED, as well as preliminary efficacy biomarkers in patients with TED. In the completed SAD portion of the study (Part A), LASN01 doses of 25, 100, 300, 600, and 1200 mg IV were evaluated. In the completed MAD portion of the study (Part B), LASN01 doses of 600 and 1200 mg IV Q2W were evaluated. The study is ongoing with planned multiple doses of 1200 mg in patients with IPF and PF-ILD (Part C) and TED (Part D). Overall, data from Parts A and B of Study LASN01-CL-1101 show favorable safety, predictable and linear PK, and target engagement in support of this Phase 2 study in TED.

This proof-of-concept Phase 2 study comprises the randomized, double-masked, placebo-controlled treatment arms in patients with TED with no prior anti-IGF-1R treatment (ie, anti-IGF-1R-naïve patients) [redacted]

The randomized treatment arms of the study will evaluate the efficacy, safety, tolerability, PK, immunogenicity, and PD of 2 dose levels of LASN01 administered IV (300 or 600 mg Q4W ×13 doses) in anti-IGF-1R-naïve TED patients. [redacted]

Objectives and Endpoints

Objectives	Corresponding Endpoints
Primary: Efficacy	
• To assess changes in proptosis following IV administration of 2 dose levels of LASN01 in patients with TED	For randomized treatment arms: • Percentage of patients who have received LASN01 (pooled analysis of 300 and 600 mg Q4W) showing a response in proptosis (≥2 mm decrease from Baseline) in the study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye at Week 37 following treatment with IV LASN01 compared with placebo [redacted]
Secondary: Efficacy	
• To assess changes in TED-related clinical parameters following IV administration of LASN01 in patients with TED	For randomized treatment arms: • Percentage of patients who have received LASN01 (600 mg Q4W) showing a response in proptosis (≥2 mm decrease from Baseline) in the study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73 following treatment with IV LASN01 compared with placebo • Percentage of patients who have received LASN01 (300 mg Q4W) showing a response in proptosis (≥2 mm decrease from Baseline) in the study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73 following treatment with IV LASN01 compared with placebo • Percentage of patients who have received LASN01 (pooled analysis of 300 and 600 mg Q4W) showing a response in proptosis (≥2 mm decrease from Baseline) in the study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye at Weeks 17, 21, 25, 29, 33, 41, 45, 49, 53, 57, 65, and 73 following treatment with IV LASN01 compared with placebo • Mean change from Baseline in proptosis in patients who have received LASN01 (600 mg Q4W) compared with placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73 • Mean change from Baseline in proptosis in patients who have received LASN01 (300 mg Q4W) compared with placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73 • Changes in TED-related clinical parameters (CAS, lid aperture, lagophthalmos, eyelid retraction, Von Graefe's sign, diplopia, extraocular movements, conjunctival redness, chemosis and lid swelling) across both LASN01 treatment arms and in each individual LASN01 treatment arm compared with placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73

Objectives	Corresponding Endpoints
[redacted]	[redacted]
Primary: Safety	
• To assess the safety and tolerability of IV administration of LASN01 in patients with TED	<u>For randomized treatment arms:</u> • Treatment-emergent adverse events, changes in concomitant medications compared with placebo • Changes from Baseline in clinical laboratory evaluations, vital signs, electrocardiograms, ophthalmic assessments, and physical examinations following study drug administration compared with placebo [redacted]
Secondary: Pharmacokinetics	
• To characterize the pharmacokinetic profile of IV administration of LASN01 in patients with TED	<u>For all treatment arms:</u> • Serum LASN01 concentrations at specified timepoints
Exploratory: Immunogenicity	
• To characterize the immunogenicity of IV administration of LASN01 in patients with TED	<u>For all treatment arms:</u> • Incidence of antidrug antibodies at specified timepoints relative to Baseline
Exploratory: Clinical	
• To assess orbital, muscle, and fat compartment volumes and confirm change in proptosis • To assess TED-related signs and confirm change in CAS, lid retraction and eye movement • To assess responder rate in TED-related clinical parameters	<u>For randomized treatment arms:</u> • MRI imaging of the orbit assessing change from Baseline in proptosis as well as orbital, muscle, and fat parameters at Week 9, 13, 29, 41, 53, and 73; LASN01 treatment arm compared to placebo • Facial imaging of the eye assessing mean values, change from earliest timepoint collected, and change from baseline (when available) in conjunctival redness, MRD1 and MRD2, and eye movement at Week 9, 13, 17, 21, 25, 29, 37, 45, 53, and 73

Objectives	Corresponding Endpoints
	• Responder analyses assessing TED-related clinical parameters in either eye 
Exploratory: Pharmacodynamics	
• To explore the potential pharmacodynamic profile of IV administration of LASN01 in patients with TED	<u>For all treatment arms:</u> • Protein markers in blood relevant to the IL-11 pathway

CAS = clinical activity score; MRD = Margin Reflex Distance; IL-11 = interleukin-11; IV = intravenous; TED = thyroid eye disease

Overall Design Synopsis

This proof-of-concept Phase 2 study comprises the randomized treatment arms and the open-label post-teprotumumab treatment arm. The randomized portion is designed as a double-masked, randomized, placebo-controlled study to evaluate the efficacy, safety, tolerability, PK, immunogenicity, and PD properties of 2 dose levels of LASN01 administered IV Q4W ×13 doses in anti-IGF-1R-naïve patients with TED. [redacted]

Following initial analysis of efficacy, the Sponsor may also expand the enrollment in the current cohorts and/or initiate additional cohorts with different subpopulations of TED patients (eg, chronic disease, recurrence following previous treatment, or in addition to standard of care). An amendment to the protocol will be submitted for appropriate regulatory authority review and/or approval in such a case.

Number of Participants

This study will include up to 36 evaluable patients with TED enrolled in 4 treatment arms. Approximately 24 anti-IGF-1R-naïve patients will be randomized (in a 1:1:1 ratio) upon enrollment to LASN01 in either a high-dose (600 mg Q4W ×13 doses) or low-dose (300 mg Q4W ×13 doses) treatment arm or to placebo [redacted] Following 48 weeks of dosing (last dose administered on Day 337), patients will be followed for an additional 24 weeks, for a total study duration of 72 weeks (EOS visit on Day 505 ± 7 days).

Enrollment Criteria

Full inclusion and exclusion criteria are provided in Section 5.1 and Section 5.2, respectively. To be enrolled in this study, all participants must meet all of the following inclusion criteria and none of the exclusion criteria. The Sponsor may request an eligibility review to review key inclusion and exclusion criteria.

Key Inclusion Criteria

Patients must have met ALL of the following inclusion criteria to be included in the study:

- Male or female ≥18 years of age at the time of Screening
- Clinical diagnosis of Graves' disease associated with active TED and a CAS of ≥4 on the CAS 7-point scale and proptosis as defined by:
  - Proptosis ≥3 mm above normal for race and gender in the more affected eye (study eye) as determined by the PI or designee and
  - Proptosis ≥19 mm in the more affected eye (study eye)
- Moderate-to-severe active TED (not sight-threatening but has an appreciable impact on daily life), as determined by the PI or designee and usually associated with ≥1 of the following: lid retraction ≥2 mm, moderate or severe soft tissue involvement, proptosis ≥3 mm above normal for race and gender, and/or inconstant or constant diplopia.

- For anti-IGF-1R-naïve patients, less than 15 months (at Day 1) from onset of TED symptoms in the study eye as determined by the PI or designee. For post-teprotumumab patients who did not respond to teprotumumab treatment for any reason, less than 24 months (at Day 1) from initial onset of TED symptoms in the study eye, as determined by the PI or designee. For post-teprotumumab patients who have reactivation of disease after responding to treatment, less than 15 months (at Day 1) from the renewed onset of TED symptoms in the study eye, as determined by the PI or designee.
- No previous:
  - Medical treatment for TED, with the exception of:
    - Local supportive measures
    - Mycophenolate, and oral or injectable steroids if the maximum cumulative dose is ≤4.5 g methylprednisolone or equivalent with ≥6 weeks between last administration of oral steroids and/or mycophenolate and Screening
    - Previous use of rituximab, tocilizumab, or any monoclonal antibody for immunomodulation, more than 9 months before Day 1
    - Previous use of any other immunomodulating therapy more than 3 months before Day 1 unless approved by the Medical Monitor
    - [redacted]
  - Surgical treatment in the study eye with the exception of routine or minor procedures at least 3 months before Screening as determined by the PI or designee
  - Any history of orbital irradiation/radiotherapy
  - Any history of orbital surgery in the study eye
- Euthyroid or with mild hypo- or hyper-thyroidism defined as free thyroxine and free triiodothyronine levels <50% above or below the normal limits (every effort should be made to correct the mild hypo- or hyper-thyroidism promptly). Patients should otherwise be on stable medical regimen and unlikely to require adjustment of thyroid medications during the 36-week treatment period as determined by the PI or designee
- Does not require immediate surgical intervention or procedure and is not planning radioactive iodine treatment during the course of the study

Key Exclusion Criteria

Patients must NOT have met any of the following exclusion criteria to be included in the study:

- Patients with 2 mm proptosis decrease between Screening and Day 1, or a 1-point decrease on the CAS 7-point scale between Screening and Day 1 and patients that no longer meet the eligibility criteria at the Day 1 ophthalmology assessment.
- Patients with a known decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 3 lines on the ETDRS chart (or equivalent), new visual

field defect, or color defect secondary to optic nerve involvement within the last 6 months before Screening; or any known optic neuropathy or compression or any neurologic or neuro-ophthalmologic condition that may result in visual field loss.

- Previous or any planned orbital irradiation/radiotherapy or planned orbital surgery for TED during the study period (ie, treatment and FU)
- Any planned procedures or hospitalizations during the study. EXCEPTION: minor or routine procedures that do not interfere with the conduct of the study may be approved by the PI or designee
- Use of oral and/or IV corticosteroid for conditions other than TED <6 weeks before Day 1 (topical steroids for conditions other than TED are allowed)
- Active autoimmune disorder(s) requiring or likely to require treatment (other than Grave's disease and TED) that would interfere with study assessments, as determined by the PI or designee
- Any liver function test result (including aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, or total bilirubin) ≥1.5× the upper limit of normal; levels may be repeated once at the discretion of the PI or designee during the Screening period or before dosing, and the lower of the 2 readings may be used (note that subjects with Gilbert's Syndrome will not be excluded)
- Previous use of an anti-IGF-1R targeted treatment at any time.
  - [redacted]
- Use of selenium within 3 weeks before Day 1 or expected use during the clinical trial (multivitamins that include selenium are allowed in usual doses)
- Use or expected use of biotin (including multivitamins that include biotin) within 2 days before any laboratory collection
- Currently receiving or have received within 4 weeks or 5 half-lives (whichever is greater) before Screening, any investigational therapy, cytotoxic, immunosuppressive, or cytokine modulating therapies; or any other therapy that, in the opinion of the PI or designee, may compromise the objectives of the study
- Infection requiring hospitalization or treatment with IV anti-infective agents within 4 weeks prior to Day 1
- Positive hepatitis B (HBV), hepatitis C (HCV) or HIV test at Screening
- History of diabetes that is not adequately controlled (ie, Hemoglobin A1c ≥8.0%)
- Platelet count <75,000/µL at Screening or within 3 months of consent
- History of malignancy within 1 year prior to Day 1 as determined by the PI or designee. EXCEPTION: patients with basal cell and squamous cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that have been completely excised or cured.

Study Arms and Duration

This study will include up to 36 evaluable patients with TED enrolled in 4 treatment arms. Approximately 24 patients will be randomized (in a 1:1:1 ratio) upon enrollment to LASN01 in either a high-dose (600 mg Q4W ×13 doses) or low-dose (300 mg Q4W ×13 doses) treatment arm or to placebo. [redacted]

Study participation (Baseline to the EOS visit) will require approximately 505 days, not including the Screening period. The Screening visit will occur up to 30 days before Day 1.

Treatment assignments will be performed centrally by IRT.

An interim analysis may be performed when at least 50% of evaluable patients in the randomized treatment arms complete at least 8 weeks in the study (details will be provided in the SAP) to inform further development. The interim analysis may also include the open-label treatment arm.

Concomitant Medications, Substances, and Therapy

Use of the following concomitant medications, substances, and therapies during the study until the EOS visit is prohibited. EXCEPTIONS: any medications that are needed as treatment for AEs are allowed as determined by the PI or designee. In such cases, the PI or designee and the Medical Monitor will determine whether the patient may continue in the study.

- Corticosteroids (oral or IV); if clinically indicated for conditions other than TED, the PI or designee should discuss with the Medical Monitor
- Rituximab, tocilizumab, teprotumumab, or any monoclonal antibody for immunomodulation
- Other immunomodulating therapy unless approved by the Medical Monitor
- Biotin (including multivitamins that include biotin) within 2 days before any laboratory collection
- Selenium

  EXCEPTION: Multivitamins that include selenium are allowed in usual doses
- Any orbital irradiation/radiotherapy or planned orbital surgery for TED.
- Vasoconstrictive eye drops and any eye drops (eg prostaglandin analogs) that can cause eye redness and swelling that impact the interpretation of study results are not permitted during the study; the use of other eye drops may be permitted if approved by the Medical Monitor. Artificial tears for dry eyes are permitted.

Note: Local supportive measures for TED, simple analgesics (eg, acetaminophen, non-steroidal anti-inflammatory therapies), and non-steroidal medications/supplements for conditions other than TED are permitted during the study. Topical corticosteroids for conditions other than TED are allowed.

Safety Review Committee

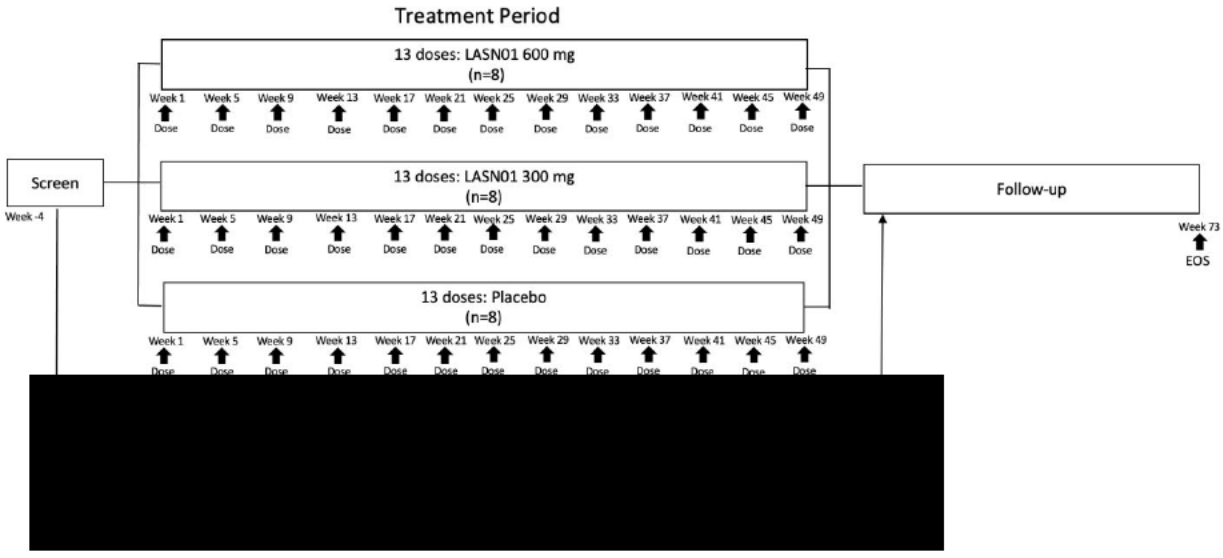
An SRC will be formed for periodic reviews of safety and available PK and PD data. For the randomized, double-blind treatment arms, the SRC will review masked data. The SRC will be minimally composed of the Medical Monitor, at least 1 study PI, and at least 1 independent member with expertise in the treatment of TED. In cases where the SRC determines that an unexpected or critical finding requires expert opinion or access to unmasked data, the SRC may refer the question to at least 3 independent experts selected by the Sponsor, including the SRC Chair, to assess the situation by reviewing necessary unmasked data and provide recommendation back to the SRC. The SRC Charter will describe the committee member structure and details for the conduct and safety review meetings.

Unmasked data may be reviewed by designated Sponsor personnel who are not responsible for study management or decisions that impact data integrity, in accordance with relevant study plans, including for interim analysis.

1.2. Schema

This proof-of-concept Phase 2 study comprises the randomized, double-masked, placebo-controlled treatment arms evaluating 2 dose levels of LASN01 to placebo and an open-label post-teprotumumab treatment arm (Figure 1). In the 3 parallel treatment arms patients will be randomized (in a 1:1:1 ratio) upon enrollment to LASN01 in either a high-dose (600 mg Q4W ×13 doses) or low-dose (300 mg Q4W ×13 doses) treatment arm or to placebo. [redacted]

Figure 1. Overall Study Design



EOS = end of study

1.3. Schedule of Activities

Table 1. Schedule of Assessments and Procedures –Treatment Period

Study Procedures	Study Day																
	Screen (Day-30 to Day-1)	1 [a]	8 (±1)	15 (±2)	29 (±3)	43 [b] (±2)	57 (±4)	85 (±4)	113 (±4)	141 (±4)	169 (±4)	197 (±4)	225 (±4)	253 (±4)	281 (±4)	309 (±4)	337 (±4)
	Week	1	2	3	5	7	9	13	17	21	25	29	33	37	41	45	49
Informed consent	X																
Demographics	X																
Inclusion/exclusion criteria evaluation	X	X															
Height (Screening only), BMI evaluation	X	X															
Body Weight	X	X			X		X	X	X	X	X	X	X	X	X	X	X
Medical history	X	X															
Complete physical examination	X																
Brief physical examination		X [c]	X	X	X [c]		X [c]	X [c]	X [c]	X [c]	X [c]	X [c]	X [c]	X [c]	X [c]	X [c]	X [c]
Pregnancy test (WOCBP) [d]	X	X [a]			X		X	X	X	X	X	X	X	X	X	X	X
Follicle-stimulating hormone as applicable [e]	X																
Urine drug screen	X																
Serology (ie, hepatitis B virus surface antigen, hepatitis C virus antibody, HIV-1, and HIV-2)	X																
12-lead ECG	X	X [f]	X		X [f]		X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]	X [f]
Vital signs [g]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
CAS [h]	X	X [a]			X		X	X	X	X	X	X	X	X	X	X	X
Proptosis measurement [v]	X	X [a]			X		X	X	X	X	X	X	X	X	X	X	X

Study Procedures	Study Day																
	Screen (Day-30 to Day-1)	**1 [a]**	**8 (±1)**	**15 (±2)**	**29 (±3)**	**43 [b] (±2)**	**57 (±4)**	**85 (±4)**	**113 (±4)**	**141 (±4)**	**169 (±4)**	**197 (±4)**	**225 (±4)**	**253 (±4)**	**281 (±4)**	**309 (±4)**	**337 (±4)**
	Week	**1**	**2**	**3**	**5**	**7**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**
Ophthalmic assessments [i]	X	X			X		X	X	X	X	X	X	X	X	X	X	X
Visual fields assessment [j]		X			X		X		X		X			X			
Color vision assessment [k]		X			X		X	X	X	X	X	X	X	X	X	X	X
Dilated fundoscopy		X										X					
Orbital MRI [l]	X						X	X				X			X		
Randomization [m]		X															
Facial photography [u]	X						X	X	X	X	X	X		X		X	
Dose (LASN01 or placebo) administration (observed for 4 hours following first dose)		X			X		X	X	X	X	X	X	X	X	X	X	X
Concomitant medications evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event evaluations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology, coagulation	X	X [n]	X	X	X [n]		X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]
Chemistry	X	X [n]	X	X	X [n]		X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]
Urinalysis	X	X [n]	X	X	X [n]		X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]
Hemoglobin A1c	X									X [n]		X [n]		X [n]			
Thyroid tests (TSH, T3, free T4)	X	X [n]			X [n]		X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]
Thyroid stimulating immunoglobulin		X [n]			X [n]			X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]
PK Assessments																	
Blood		X [o]	X	X	X [o]				X [o]			X [o]		X [o]-			X [o]

Study Procedures	Study Day																
	Screen (Day-30 to Day-1)	**1 [a]**	**8 (±1)**	**15 (±2)**	**29 (±3)**	**43 [b] (±2)**	**57 (±4)**	**85 (±4)**	**113 (±4)**	**141 (±4)**	**169 (±4)**	**197 (±4)**	**225 (±4)**	**253 (±4)**	**281 (±4)**	**309 (±4)**	**337 (±4)**
	Week	**1**	**2**	**3**	**5**	**7**	**9**	**13**	**17**	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**
Immunogenicity Assessments																	
ADA		X [p]			X [p]		X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]
PD Assessments																	
Blood sample for markers relevant to TED		X [q]	X		X [q]		X [q]	X [q]	X [q]			X [q]		X [q]			X [q]
Blood sample for analysis of IL-11		X [r]	X	X	X [r]		X [r]	X [r]	X [r]			X [r]		X [r]			X [r]
Blood sample for analysis of IL-11R		X [r]	X	X	X [r]		X [r]	X [r]	X [r]			X [r]		X [r]			X [r]

Table 1b. Schedule of Assessments and Procedures – Follow-up Period

Study Procedures	Study Day						
	344 (±4)	351 (±4)	365 (±4)	379 (±4)	393 (±4)	449 (±7)	505 (±7) EOS/ET [t]
	Week 50	Week 51	Week 53	Week 55	Week 57	Week 65	Week 73
Height (Screening only), BMI evaluation							
Body Weight			X		X	X	X
Complete physical examination							X
Brief physical examination			X		X	X	
Pregnancy test (WOCBP)			X				X [d]
12-lead ECG							X
Vital signs [g]			X		X	X	X
CAS [h]			X		X	X	X
Proptosis measurement [v]			X		X	X	X
Ophthalmic assessments [i]			X		X	X	X
Visual fields assessment [j]			X				X
Color vision assessment			X		X	X	X
Dilated fundoscopy							X
Orbital MRI [l]			X				X
Facial photography [u]			X				X
Concomitant medications evaluation	X	X	X	X	X	X	X
Adverse event evaluations	X	X	X	X [s]	X [s]	X [s]	X [s]
Hematology, coagulation			X				X
Chemistry			X				X
Urinalysis			X				X
Hemoglobin A1c			X				X
Thyroid tests (TSH, T3, free T4)			X		X	X	X
Thyroid stimulating immunoglobulin			X		X	X	X
PK Assessments							
Blood	X [o]	X	X	X	X		X
Immunogenicity Assessments							
ADA			X		X	X	X

Study Procedures	Study Day						
	344 (±4)	351 (±4)	365 (±4)	379 (±4)	393 (±4)	449 (±7)	505 (±7) EOS/ET [t]
	Week 50	Week 51	Week 53	Week 55	Week 57	Week 65	Week 73
PD Assessments							
Blood sample for markers relevant to TED			X				X
Blood sample for analysis of IL-11			X				X
Blood sample for analysis of IL-11R			X				X

ADA = antidrug antibody; BMI = body mass index; CAS = clinical activity score; ECG = electrocardiogram; EOS = End of Study; ET = Early Termination; HIV = human immunodeficiency virus; IL-11 = interleukin-11; IL-11R = interleukin-11 receptor; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; PD = pharmacodynamic; PK = pharmacokinetic; TED = thyroid eye disease; WOCBP = women of childbearing potential

a. Day 1 assessments are performed within 3 days before study drug dosing unless otherwise specified. Day 1 ophthalmology assessments (ie, CAS and proptosis measurement) and urine pregnancy test should be used to confirm eligibility before first dose is administered.
b. Safety assessments (concomitant medications and adverse events evaluation) on Day 43 may be completed by telephone call if appropriate
c. Brief physical examination should be performed predose on dosing days
d. A serum pregnancy test should be performed at Screening and at EOS/ET (Day 505). A urine pregnancy test should be performed at all other specified clinic visits. Urine pregnancy test should be performed predose on dosing days
e. For female patients who are postmenopausal to confirm that they are not WOCBP
f. Triplicate 12-lead ECG should be performed predose on dosing days. Perform triplicate ECGs within a 15-minute period, separated by ≥1 minute. ECG recordings will be taken after ≥5 minutes in a semi-supine, quiet-rest position (head of bed between 0° and 90°), and before obtaining any blood sample. Refer to Section 8.2.7 for details.
g. Vital signs include seated respiratory rate, blood pressure, pulse rate, and body temperature. Vital signs will be measured predose and post-dose on Day 1 and predose on all other dosing days. Additional vital signs will be monitored if infusion-associated AEs or other AEs occur at PI discretion (see Section 8.2.6 for details). Vital signs on nondosing visits should be taken at approximately the same time (±2 hours) as taken on dosing days, whenever possible. Note that the timing of PK samples should take priority over the timing for vital signs.
h. The same assessor should conduct each CAS evaluation at each visit. Refer to Section 8.1.2 for details on orbital pain, conjunctival redness, eyelid swelling and chemosis grading in addition to CAS score. CAS assessment should be completed prior to any eye drops administered for dilation or any other purpose. CAS should be assessed predose on dosing days.
i. Lid aperture, visual acuity, diplopia and extraocular movements, lid retraction, lagophthalmos, Von Graefe's sign, slit lamp biomicroscopy, and intraocular pressure should be assessed predose on dosing days
j. Visual fields should be assessed predose on dosing days. In the event of elevated IOP or AEs potentially related to decreased optic nerve function, additional visual fields may be assessed at PI discretion.
k. Ishihara color vision assessment should be assessed predose on dosing days
l. Exception: Patients who cannot have an MRI due to the presence of metal or other known reason. In the US only, an orbital CT scan may be performed in patients who cannot have an MRI. In such cases all imaging time points must have a CT scan performed. Images collected within 30 days of consent as part of standard of care may be used as the Baseline scan, provided that the acquired image conforms to the study-specific image acquisition parameters and with prior approval from the Medical Monitor.

m. Randomization will take place by IRT after all eligibility criteria are met and not more than 3 days before dosing
n. Safety laboratory samples should be obtained predose
o. PK samples should be obtained predose on the specified dosing days in the schedule of assessments above. On Days 1 and 337, samples should also be obtained 30-60 minutes after the end of the infusion. On Day 344, the sample should be collected at a similar time of day when the Day 337 post dose sample collection occurred.
p. ADA samples should be obtained predose on the specified dosing days in the schedule of assessments above. On Day 1, samples should also be obtained at end of infusion (≤60 minutes after the end of the infusion).
q. Blood samples for exploratory biomarkers relevant to TED, fibrosis, and inflammation should be collected predose on the specified dosing days in the schedule of assessments above.
r. Serum for analysis of IL-11 and IL-11R should be obtained predose on the specified dosing days in the schedule of assessments above. On Days 1 and 337, serum samples should also be obtained 30-60 minutes after the end of the infusion.
s. Treatment-emergent adverse events should be captured until Week 53 (Day 365). From this visit to the EOS/ET (Week 73: Day 505) visit, only treatment-related AEs should be recorded.
t. Patients who prematurely discontinue study drug should still remain on study for scheduled visits and assessments and every effort should be made to obtain protocol-specified assessments. Patients who withdraw completely from this clinical study should be encouraged to complete the EOS/ET visit.
u. Facial photographs (including retrospective facial photographs) should be collected only after informed consent is obtained. The five cardinal positions of gaze (up, down, right, left and primary gaze) should be captured.
v. The same instrument and assessor should be used for each visit. If a different assessor than the initial/main assessor is used, then the assessment should be repeated by the initial/main assessor as soon as possible.

2. INTRODUCTION

LASN01 is a first-in-class, fully human, IgG4κ monoclonal antibody directed against human IL-11R and is being initially developed for treatment of patients with TED.

2.1. Study Rationale

2.1.1. Unmet Need in TED

Despite extensive ongoing research, the pathophysiology, prevention, and ideal treatment for TED remains elusive (Rashad 2022; Supronik 2022). Teprotumumab (TEPEZZA®) is an insulin-like growth factor-1 receptor inhibitor approved in the United States in 2020 for the treatment of TED (Teprotumumab Prescribing Information 2022). Warnings and precautions include infusion reactions, exacerbation of preexisting inflammatory bowel disease, and hyperglycemia. Severe cases of TED require aggressive measures to manage the patient's systemic thyroid disorder. Intravenous glucocorticosteroid therapy continues to be generally used as first-line treatment for moderate to severe acute TED in the rest of the world, but efficacy is often underwhelming, the rate of recurrence is high, and there are significant side effects. The recent EUGOGO guidelines propose that mycophenolate be added to IV glucocorticosteroid therapy as a first-line treatment in active, moderate-to-severe Graves' orbitopathy, considering its beneficial effect on long-term outcome and less frequent recurrences (Bartalena 2021). Considering the complex pathogenesis of TED involving many molecular pathways, a number of agents are proposed as a second-line treatment in the event of poor response to IV teprotumumab or glucocorticosteroid therapy or disease relapse after treatment. Novel agents with different mechanism of action are needed in the treatment of TED.

2.1.2. IL-11 Activation of Fibroblasts and Tissue Fibrosis

IL-11R is a 422 amino acid type I transmembrane protein that is the sole known receptor for IL-11. In common with other members of the IL-6 cytokine family, IL-11 signaling uses a common co-receptor, gp130 (also known as IL6ST). IL-11 signaling takes place upon binding of IL-11 to IL-11R followed by recruitment of gp130 into a hexameric signaling complex containing 2 molecules each of IL-11, IL-11R, and gp130 (Barton 2000). Resultant signaling takes place through both the phosphorylation of STAT3 and of ERK (Metcalfe 2020; Widjaja 2019). LASN01 inhibits signaling with pM potency through binding specifically to IL-11R and inhibiting its ability to form a functional signaling complex with gp130, hence preventing IL-11-induced signaling.

IL-11 signaling has been shown to be an important regulator of fibroblast activation and tissue fibrosis. This was demonstrated as early as 1996, when IL-11 overexpression in the airways of mice was shown to result in tissue fibrosis and the potentiation of tissue inflammation (Tang 1996). Since then, a role has been suggested in a number of human fibroinflammatory diseases as described below.

IL-11 is stimulated by and exhibits crosstalk with other fibroinflammatory mediators such as TGFβ, platelet-derived growth factor, connective tissue growth factor, Ang II, and IL-13 (Ng 2020; Kortekaas 2021; Schafer 2017). In interstitial lung diseases, IL-11 expression has

been reported to be increased in tissue from patients with IPF (Ng 2019) and also significantly upregulated in invasive IPF fibroblasts compared to healthy controls (Geng 2019). Similarly, IL-11 was one of the most highly upregulated genes in tissue from scleroderma-associated interstitial lung disease patients (Lindahl 2013). In the heart, RNAseq data on cardiac fibroblasts from 84 independent donors revealed that IL-11 was highly upregulated following TGFβ treatment, and IL-11R knock-out mice were protected in an angiotensin II-induced cardiac fibrosis model (Schafer 2017). Similar correlations between IL-11 expression and tissue fibrosis have been noted in nonalcoholic steatohepatitis, kidney disease, ulcerative colitis, and Hermansky Pudlak Syndrome (Widjaja 2019; Menendez-Castro 2020; Nishina 2021; Strikoudis 2019). These data indicate that IL-11 is a prominent fibroinflammatory mediator and suggests that inhibition of IL-11 signaling may provide a novel therapeutic approach to treat fibroinflammatory diseases.

2.2. Background

2.2.1. TED

TED, also known as Graves' orbitopathy or Graves' eye disease, is an inflammatory disorder of orbital tissue characterized by infiltration of lymphocytic cells, orbital fat expansion, and extraocular muscle swelling (Rashad 2022; Supronik 2022). It is associated with the systemic disease hyperthyroidism which requires a multimodal approach to treatment in addition to the treatment of TED. Treatment of the systemic disease can also impact TED so patients with hyperthyroidism with or without TED should also engage in smoking cessation and other measures to treat the hyperthyroidism.

TED is an autoimmune disorder, with associated thyroid autoimmunity always discernible. The presence of one or more shared autoantigens between the thyroid and the orbit may explain why retro-orbital tissues are affected. Extraocular muscles and retro-ocular connective tissue are infiltrated by lymphocytes, leading to activation of cytokine networks and inflammation and interstitial edema of the extraocular muscles. Excess secretion of glycosaminoglycans by orbital fibroblasts seems to be an important contributor. The end result is expansion of the volume of extraocular muscles, retro-orbital fat, and connective tissue. Similar changes affect the eyelids and anterior periorbital tissues. Apart from visible swelling and redness of the eyelids and conjunctiva, the other clinical features of thyroid eye disease can also be accounted for by the expansion of inflammatory soft tissue within the constraints of the rigid bony orbit. Anterior displacement of the globe by the edematous extraocular muscles and orbital fibrofatty tissues results in exophthalmos and lower lid retraction. These symptoms in turn may lead to impaired lid closure and significant ocular surface disease including corneal ulceration, especially if the levator muscle is also infiltrated and its excursion restricted. Edematous extraocular muscles lose compliance, restrict eye movements, and can compress the optic nerve at the orbital apex (Perros 2009).

The incidence of clinically relevant TED is 16 per 100,000 in females and 2.9 per 100,000 in males. Overall, TED is a sight-threatening, debilitating, disfiguring disease that can profoundly affect quality of life. Other supportive measures that do not bias the assessments in this trial are

encouraged including local treatment of ocular surface disease (dry eye, exposure, keratopathy, and corneal ulceration) with dry eye drops and lubricant ointments and antibiotics or other medical therapy as needed. It is also generally recommended that all patients with TED cease smoking.

2.2.2. LASN01

LASN01 is a first-in-class, fully human, IgG4κ monoclonal antibody directed against human IL-11R that has demonstrated compelling antifibrotic activity in nonclinical studies and is in development for the treatment of patients with TED. Detailed information on LASN01 is provided in the LASN01 IB.

2.2.2.1. Nonclinical Summary

[redacted]

2.2.2.1.1. Mode of Action

IL-11 signaling has been demonstrated to be mediated by binding of IL-11 to IL-11R, followed by subsequent recruitment of gp130, leading to formation of a ternary complex and functional signaling through the STAT3 or ERK pathway (Dahmen 1998). Via this signaling mechanism, IL-11 induces downstream phosphorylation of STAT3 and ERK pathways with subsequent effects on cellular proliferation, survival, migration/invasion, angiogenesis, and differentiation (Johnstone 2015).

LASN01 is a first-in-class monoclonal antibody that binds to IL-11R to block IL-11 signaling. The IL-11R is a novel target with a central role in fibrotic signaling.

2.2.2.1.2. Nonclinical Pharmacology

[redacted]

- [redacted]

[redacted]

2.2.2.1.3. Nonclinical PK

[redacted]

2.2.2.2. Nonclinical Safety Pharmacology

[redacted]

2.2.2.2.1. Nonclinical Toxicology

[redacted]

2.2.2.2.2. Immunogenicity

[redacted]

2.2.2.2.3. Genotoxicity

No genotoxicity studies are required since LASN01 is a monoclonal antibody.

2.2.2.2.4. Reproductive Toxicity

No reproductive toxicity studies have been conducted to date.

2.2.2.3. Clinical Summary

A first-in-human 4-part Phase 1/2a (LASN01-CL-1101) randomized, double-blind placebo-controlled, SAD, and MAD clinical study is ongoing in Australia to determine the safety, tolerability, preliminary efficacy, immunogenicity, and PK properties of LASN01 in healthy volunteers and in patients with pulmonary fibrosis or TED, as well as preliminary efficacy biomarkers in patients with TED.

In the healthy volunteer portions of the study (ie, SAD and MAD cohorts), interim, topline, unblinded safety and PK data for 58 healthy volunteers are available (data cutoff date of 02JUN2023). In the completed SAD portion of the study (Part A), LASN01 doses of 25, 100, 300, 600, and 1200 mg IV were evaluated. In the completed MAD portion of the study (Part B), LASN01 doses of 600 (B1) and 1200 (B2) mg IV were evaluated. The study is ongoing with planned multiple doses of 1200 mg in patients with IPF and PF-ILD (Part C) and TED (Part D).

Overall, 35 healthy volunteers (60.3%) experienced 61 TEAEs. A total of 13 healthy volunteers (22.4%) experienced 18 TEAEs considered potentially related to study drug (LASN01 or placebo) by the Investigator. There were no serious or severe TEAEs reported and no subject withdrew from the study due to a TEAE. The incidence of TEAEs was not dose related. Most TEAEs were not related to study drug and all were mild or moderate in severity.

The PK of LASN01 follows approximately dose-proportional PK based on both the SAD and MAD cohorts. The mean half-life estimates ranged from 165 to 335 hours at doses ≥25 mg/day administered as a single IV dose or as 2 administrations 14 days apart, supporting the extended dosing intervals under consideration for clinical studies. The PK profile in healthy volunteers is consistent with that observed in the cynomolgus monkey.

Subject samples from all cohorts reduced the ability of hyper IL-11 to stimulate phosphorylated STAT3 signal 24 hours after dosing in both the T-cell and monocyte populations to Baseline levels. The duration of inhibition of phosphorylated STAT3 signal demonstrated a time-dependent and dose-dependent relationship.

Overall, data from Parts A and B of Study LASN01-CL-1101 show favorable safety, predictable and linear PK, and target engagement in support of this Phase 2 study in TED. Part C and D have completed enrollment and these parts are ongoing. Ongoing safety surveillance of the masked patients in Parts C and D does not show any further safety signals and appears to have a similar safety profile to Parts A and B.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

As this is the second clinical trial of LASN01 in humans, a full risk profile has not yet been characterized. In the Phase 1/2a clinical study (LASN01-CL-1101), no safety concerns have emerged to date. Patients in Parts C and D in the study have completed enrollment and are ongoing without additional safety signals observed with ongoing safety monitoring. Nonclinical studies and data from humans with genetic defects in IL-11 production show defects in bone development (Nieminen 2011; Keupp 2013). Short-term exposures in adult patients in the proposed study are not expected to cause any developmental defects. Inhibition of fibrogenesis can potentially affect normal wound healing (Allanki 2021). However, IL-11 is not known to affect normal fibrotic processes or normal wound healing. Recombinant IL-11 is an approved treatment that stimulates thrombopoiesis. However, IL-11 knockout animals do not display platelet defects, and LASN01 and IL-11 have shown no effect on platelet numbers or function in nonclinical toxicology studies (Section 2.2.2.2.1). Liver function tests will be followed closely for any clinically significant, adverse changes.

An additional internal Lassen Therapeutics study investigated the ability of LASN01 to induce cytokine release in vitro using either peripheral blood mononuclear cells or whole blood. Results show that LASN01 has a low probability of inducing cytokine release in patients. In the subsequent healthy volunteer Phase 1 trial, no symptoms of cytokine release were observed in any of the patient cohorts, including the high dose of 1200 mg.

Data is pending on the effects of LASN01 withdrawal on the levels of IL-11 in circulation.

To ensure the safety of all patients, safety data will be closely followed for all patients.

No reproductive toxicity studies have been performed with LASN01. Based on published literature, reproductive development toxicity has been observed in IL-11 knockout mice. In contrast, humans with genetic mutations resulting in impaired IL-11R function appear fertile, despite displaying developmental effects such as a craniosynostosis-like phenotype (Keupp 2013). These data suggest fertility effects may be species specific.

This study requires female patients to be nonpregnant, nonlactating, and either postmenopausal, surgically sterile, or agree to use highly effective forms of contraception (Appendix 4, Section 10.4). Males must be surgically sterile or agree to highly effective methods of contraception (Clinical Trials Facilitation and Coordination Group 2020) (Appendix 4, Section 10.4).

2.3.2. Benefit Assessment

This is the first Phase 2 study in patients with TED; the clinical benefit of LASN01 in patients with TED has not yet been evaluated. Patients with TED who receive LASN01 may experience improvement in signs and symptoms of disease.

2.3.3. Overall Benefit Risk Conclusion

Based on the currently available nonclinical and clinical data, LASN01 is anticipated to have a favorable benefit to risk profile in patients with TED. The efficacy of LASN01 has been established in vitro and in animal models (Section 2.2.2.1.2).

In the first-in-human, Phase 1, clinical study (LASN01-CL-1101) in healthy volunteers, no safety concerns have emerged to date and no serious or severe AEs were reported. Enrollment of patients with IPF/PF-ILD (Part C) or TED (Part D) is completed and the study is ongoing to evaluate the safety and preliminary efficacy of LASN01 at 1200 mg with a favorable safety profile to date.

Overall, the non-clinical and clinical safety profile of LASN01 remains favorable and supports continued development of LASN01 in patients with TED.

Frequent monitoring of safety data will be performed, with timely review and safety monitoring will be adjusted as required if any risks become apparent. An SRC will review safety data on an ongoing basis.

3. OBJECTIVES AND ENDPOINTS

Objectives	Corresponding Endpoints
Primary: Efficacy	
• To assess changes in proptosis following IV administration of 2 dose levels of LASN01 in patients with TED	For randomized treatment arms: • Percentage of patients who have received LASN01 (pooled analysis of 300 and 600 mg Q4W) showing a response in proptosis (≥2 mm decrease from Baseline) in the study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye at Week 37 following treatment with IV LASN01 compared with placebo [redacted]
Secondary: Efficacy	
• To assess changes in TED-related clinical parameters following IV administration of LASN01 in patients with TED	For randomized treatment arms: • Percentage of patients who have received LASN01 (600 mg Q4W) showing a response in proptosis (≥2 mm decrease from Baseline) in the study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73 following treatment with IV LASN01 compared with placebo • Percentage of patients who have received LASN01 (300 mg Q4W) showing a response in proptosis (≥2 mm decrease from Baseline) in the study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73 following treatment with IV LASN01 compared with placebo • Percentage of patients who have received LASN01 (pooled analysis of 300 and 600 mg Q4W) showing a response in proptosis (≥2 mm decrease from Baseline) in the study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye at Weeks 17, 21, 25, 29, 33, 41, 45, 49, 53, 57, 65, and 73 following treatment with IV LASN01 compared with placebo • Mean change from Baseline in proptosis in patients who have received LASN01 (600 mg Q4W) compared with placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73 • Mean change from Baseline in proptosis in patients who have received LASN01 (300 mg Q4W) compared with placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73 • Changes in TED-related clinical parameters (CAS; lid aperture; lagophthalmos, eyelid retraction, Von Graefe's sign; diplopia and extraocular movements, conjunctival redness, chemosis and lid swelling) across both LASN01 treatment arms and in each individual LASN01 treatment arm compared with placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73

Objectives	Corresponding Endpoints
[redacted]	[redacted]
Primary: Safety	
• To assess the safety and tolerability of IV administration of LASN01 compared with placebo in patients with TED	<u>For randomized treatment arms:</u> • Treatment-emergent adverse events, changes in concomitant medications compared with placebo • Changes from Baseline in clinical laboratory evaluations, vital signs, electrocardiograms, ophthalmic assessments, and physical examinations following study drug administration compared with placebo [redacted]
Secondary: Pharmacokinetics	
• To characterize the pharmacokinetic profile of IV administration of LASN01 in patients with TED	<u>For all treatment arms:</u> • Serum LASN01 concentrations at specified timepoints
Exploratory: Immunogenicity	
• Characterize the immunogenicity of IV administration of LASN01 in patients with TED	<u>For all treatment arms:</u> • Incidences of antidrug antibodies at specified timepoints relative to Baseline
Exploratory: Clinical	
• To assess orbital, muscle, and fat compartment volumes and confirm change in proptosis • To assess TED-related signs and confirm change in CAS, lid retraction and eye movement • To assess responder rate in TED-related clinical parameters	<u>For randomized treatment arms:</u> • MRI imaging of the orbit assessing change from Baseline in proptosis as well as in orbital, muscle, and fat parameters at Week 9, 13, 29, 41, 53, and 73; LASN01 treatment arm compared to placebo • Facial imaging of the eye assessing mean values, change from earliest timepoint collected, and change from baseline (when available) in conjunctival redness, MRD1 and MRD2, and eye movement at Week 9, 13, 17, 21, 25, 29, 37, 45, 53, and 73

Objectives	Corresponding Endpoints
	• Responder analyses assessing TED-related clinical parameters in either eye 
Exploratory: Pharmacodynamics	
• To explore the potential pharmacodynamic profile of IV administration of LASN01 in patients with TED	<u>For all treatment arms:</u> • Protein markers in blood relevant to the IL-11 pathway

CAS = clinical activity score; IL-11 = interleukin-11; IV = intravenous; TED = thyroid eye disease

4. STUDY DESIGN

4.1. Overall Design

This proof-of-concept Phase 2 comprises the randomized, double-masked, placebo-controlled treatment arms in patients with TED with no prior anti-IGF-1R treatment (ie, anti-IGF-1R-naïve patients) [redacted]

The randomized treatment arms will evaluate the efficacy, safety, tolerability, PK, immunogenicity, and PD of 2 dose levels of LASN01 administered IV Q4W ×13 doses in anti-IGF-1R-naïve patients with TED. [redacted]

Following initial analysis of efficacy, the Sponsor may also expand the enrollment in the current cohorts and/or initiate additional cohorts with different subpopulations of TED patients (eg, chronic disease, recurrence following previous treatment, or in addition to standard of care). An amendment to the protocol will be submitted for appropriate regulatory authority review and/or approval in such a case.

This study will include approximately 36 evaluable patients with TED in 4 treatment arms. For the randomized treatment arms, approximately 24 patients will be randomized (in a 1:1:1 ratio) upon enrollment to LASN01 in either a high-dose (600 mg Q4W ×13 doses) or low-dose (300 mg Q4W ×13 doses) treatment arm or to placebo. [redacted]

The Schedule of Assessments and Procedures is presented in Section 1.3 and the study schematic is presented in Figure 1. The Screening period will last up to 30 days before Day 1, the treatment period will last 48 weeks, and the FU period will last approximately 24 additional weeks. The Medical Monitor may extend the Screening period by up to 7 business days if needed to accommodate logistical delays. This study is outpatient and does not require admission to a clinical research unit.

Table 2. Multiple Dose Study Design

Randomized Treatment Arm	Dose	Number of Doses	Number of Patients
1	Low-dose LASN01 (300 mg Q4W)	13	8
2	High-dose LASN01 (600 mg Q4W)	13	8
3	Placebo (Q4W)	13	8
		Total Number of Patients	24

[redacted]

4.2. Justification for Dose

[redacted]

4.3. Rationale for Comparator

In this study, placebo will be used as a comparator to demonstrate the treatment effect of LASN01 in patients with TED. Safety monitoring during the study will include regular ophthalmic examinations and the patient's TED will be monitored closely to ensure safety.

[redacted]

4.5. End of Study Definition

A patient is considered to have completed the study if the patient has completed all periods of the study including the EOS visit. The study will be defined as ended for all patients as of the date of the EOS visit of the last patient.

5. STUDY POPULATION

In this study, patients with TED meeting all study eligibility criteria will be included. Regulatory, ethical, and study oversight consideration are provided in Appendix 1 (Section 10.1).

To be enrolled in this study, all participants must meet all of the following inclusion criteria and none of the exclusion criteria. The Sponsor may request an eligibility review to review key inclusion and exclusion criteria.

5.1. Inclusion Criteria

Patients must have met ALL of the following inclusion criteria to be included in the study:

1. Male or female patients ≥18 years of age at the time of Screening
2. Clinical diagnosis of Graves' disease associated with active TED and a CAS of ≥4 on the CAS 7-point scale and proptosis as defined by:
    - Proptosis ≥3 mm above normal for race and gender in the more affected eye (study eye) as determined by the PI or designee and
    - Proptosis ≥19 mm in the more affected eye (study eye)
3. Moderate-to-severe active TED (not sight-threatening but has an appreciable impact on daily life) determined by the PI or designee, usually associated with ≥1 of the following: lid retraction ≥2 mm, moderate or severe soft tissue involvement, proptosis ≥3 mm above normal for race and gender, and/or inconstant or constant diplopia
4. For anti-IGF-1R-naïve patients: less than 15 months (at Day 1) from onset of TED symptoms in the study eye as determined by the PI or designee. For post-teprotumumab patients who did not respond to teprotumumab treatment for any reason, less than 24 months (at Day 1) from initial onset of TED symptoms in the study eye, as determined by the PI or designee. For post-teprotumumab patients who have reactivation of disease after responding to treatment, less than 15 months (at Day 1) from the renewed onset of TED symptoms in the study eye, as determined by the PI or designee.
5. No previous:
    - Medical treatment for TED, with the exception of:
        - Local supportive measures
        - Mycophenolate, and oral or injectable steroids if the maximum cumulative dose is ≤4.5 g methylprednisolone or equivalent with ≥6 weeks between last administration of oral steroids and/or mycophenolate and Screening
        - Previous use of rituximab, tocilizumab, or any monoclonal antibody for immunomodulation, more than 9 months before Day 1
        - Previous use of any other immunomodulating therapy more than 3 months before Day 1 unless approved by the Medical Monitor

- [redacted]
- Surgical treatment in the study eye with the exception of routine or minor procedures at least 3 months before Screening as determined by the PI or designee
- Any history of orbital irradiation/radiotherapy
- Any history of orbital surgery in the study eye

6. Euthyroid or with mild hypo- or hyper-thyroidism defined as free thyroxine and free triiodothyronine levels <50% above or below the normal limits (every effort should be made to correct the mild hypo- or hyper-thyroidism promptly). Patients should otherwise be on stable medical regimen and unlikely to require adjustment of thyroid medications during the 36-week treatment period as determined by the PI or designee.
7. Does not require immediate surgical intervention or procedure and is not planning radioactive iodine treatment during the course of the study
8. WOCBP patients with male partners and WOCBP partners of male patients must be nonpregnant, nonlactating, use a highly effective method of contraception, unless considered permanently surgically sterile for ≥6 months (ie, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), from the start of the study and for ≥90 days following the last dose of study drug or until the EOS visit, whichever is later. Males must use a highly effective method of contraception unless considered permanently surgically sterile following a bilateral orchidectomy (Clinical Trials Facilitation and Coordination Group 2020) (Appendix 4, Section 10.4).
9. Able to comprehend and willing to sign an ICF and understand and comply with the requirements of the study

5.2. Exclusion Criteria

Patients must NOT have met any of the following exclusion criteria to be included in the study:

1. Patients with 2 mm proptosis decrease between Screening and Day 1, or a 1-point decrease on the CAS 7-point scale between Screening and Day 1 and patients that no longer meet the eligibility criteria at the Day 1 ophthalmology assessment.
2. Patients with a known decreased best corrected visual acuity due to optic neuropathy as defined by a decrease in vision of 3 lines on the ETDRS chart (or equivalent), new visual field defect, or color defect secondary to optic nerve involvement within the last 6 months before Screening; or any known optic neuropathy or compression or any neurologic or neuro-ophthalmologic condition that may result in visual field loss.
3. Previous or any planned orbital irradiation/radiotherapy or planned orbital surgery for TED during the study period (ie, treatment and FU)
4. Any planned procedures or hospitalizations during the study. EXCEPTION: minor or routine procedures that do not interfere with the conduct of the study may be approved by the PI or designee

5. Poor peripheral venous access that would preclude study assessments
6. Use of oral and/or IV corticosteroid for conditions other than TED in the 6 weeks before Day 1 (topical steroids for conditions other than TED are allowed)
7. Active autoimmune disorder(s) requiring or likely to require treatment (other than Grave's disease and TED) that would interfere with study assessments, as determined by the PI or designee
8. Any liver function test result (including aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, or total bilirubin) ≥1.5× the upper limit of normal; levels may be repeated once at the discretion of the PI or designee during the Screening period or before dosing, and the lower of the 2 readings may be used (note that subjects with Gilbert's Syndrome will not be excluded)
9. Previous use of an anti-IGF-1R targeted treatment at any time.
    a. [redacted]
10. Use of selenium within 3 weeks before Day 1 or expected use during the clinical trial (multivitamins that include selenium are allowed in usual doses)
11. Use or expected use of biotin (including multivitamins that include biotin) within 2 days before any laboratory collection
12. Receipt of blood products within 2 months before Day 1
13. Donation of blood >400 mL within 30 days before Day 1 or planned through EOS visit, inclusive, or plasma >400 mL within 7 days before Day1 through EOS visit, inclusive
14. Current or history of drug or alcohol abuse within the previous 2 years in the opinion of the PI or as reported by the patient
15. Known hypersensitivity to any of the components of LASN01 or placebo formulations or previous hypersensitivity to monoclonal antibodies
16. Previous participation in a study investigating LASN01
17. Currently receiving or have received within 4 weeks or 5 half-lives (whichever is greater) before Screening, any investigational therapy, cytotoxic, immunosuppressive, or cytokine modulating therapies; or any other therapy that, in the opinion of the PI, may compromise the objectives of the study
18. Any acute or chronic condition or any other reason that, in the opinion of the PI, would limit the patient's ability to participate in and complete this clinical study
19. Infection requiring hospitalization or treatment with IV anti-infective agents within 4 weeks prior to Day 1
20. Positive hepatitis B (HBV), hepatitis C (HCV) or HIV test at Screening
21. History of diabetes that is not adequately controlled (ie, Hemoglobin A1c ≥8.0%)
22. Platelet count <75,000/µL at Screening or within 3 months of consent

23. History of malignancy within 1 year prior to Day 1 as determined by the PI or designee. EXCEPTION: patients with basal cell and squamous cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that have been completely excised and cured.

5.3. Requalification and Rescreening for Entry

During the Screening period, procedures may be repeated, if appropriate, and at the discretion of the PI or designee. For patients who fulfill entry criteria but are not randomized within the 30-day Screening visit window, the patient may still be eligible; the Medical Monitor will determine which procedures from the original Screening period can be used and which procedures must be repeated to confirm eligibility.

Patients not fulfilling the entry criteria and not randomized may be rescreened once if reconsidered for study participation.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

LASN01 drug product is supplied as a sterile, colorless to pale brown frozen liquid for thawing and dilution with WFI before infusion (Table 3). Each vial of LASN01 drug product is comprised of 100 mg of LASN01. Excipients are 20 mM histidine, 200 mM arginine, 125 mM sorbitol, and 0.02% (v/v) polysorbate 20. The product is limited to investigational use only.

Pharmaceutical grade 0.9% sodium chloride will be administered IV as the placebo control.

Table 3. Study Intervention(s) Administered

Intervention Name	Low-dose LASN01 (300 mg)	High-dose LASN01 (600 mg)	Placebo
Intervention Description	Antibody	Antibody	0.9% sodium chloride
Type	Biological	Biological	0.9% sodium chloride
Unit Dose Strength(s)	20 mg/mL	20 mg/mL	Not applicable
Total Volume Administered	60 mL Bag 1: 30-mL placebo Bag 2: 15-mL LASN01 + 15-mL Water for Injection	60 mL Bag 1: 15-mL LASN01 + 15 mL Water for Injection Bag 2: 15-mL LASN01 + 15 mL Water for Injection	60 mL Bag 1: 30-mL placebo Bag 2: 30-mL placebo
Storage of Prepared Investigational Product	Prepared infusion bags should be stored in 1 of 2 conditions: 1) 2°C to 8°C for no more than 24 hours total OR 2) Room temperature for no more than 6 hours		
Route of Administration	Intravenous infusion	Intravenous infusion	Intravenous infusion

6.2. Shipping, Storage, Preparation, Handling, and Accountability

Each shipment of LASN01 is transferred to the sites on dry ice and will contain a drug transmittal and receipt form to assist in maintaining current and accurate inventory records. Upon receipt of LASN01, the pharmacy or study personnel will visually inspect the shipment and verify the number and condition of vials received. The vials are immediately transferred to the storage unit. Vials of LASN01 Solution for Injection are stored at ≤ -60°C and protected from light.

Vialed LASN01 drug product is thawed and diluted with WFI according to Table 3. Once the IP dose has been prepared in the infusion bags, the bags should be stored at 2°C to 8°C for no more than 24 hours total, or at room temperature for no more than 6 hours.

LASN01 is infused at a rate of 200mL/hr using an in-line 0.2-micron filter. Pharmaceutical grade 0.9% sodium chloride will be delivered as a line flush after IP infusion.

Similarly, the placebo will follow the details outlined in (Table 3). Placebo will also use an in-line 0.2-micron filter. The pharmacy or unmasked study personnel are responsible for ensuring that a current record of LASN01 inventory and accountability is maintained. An unmasked Pharmacy Monitor will be responsible for checking drug accountability at the site. Inventory and accountability records must be readily available for inspection by the unmasked Pharmacy Monitor and are open to inspection at any time by applicable regulatory authorities.

Final drug disposition procedures will be detailed in the applicable study manuals.

Please refer to the Pharmacy Manual for detailed information on study drug storage, preparation, handling, and accountability.

6.3. Assignment to Study Intervention

Patients will be assigned a Screening Number at signing of the ICF.

For the randomized treatment arms, patients will be randomized to receive LASN01 300 mg, LASN01 600 mg, or placebo. Patients are confirmed as eligible for randomization based on Screening assessments. Randomization should take place not more than 3 days before dosing. Day 1 assessments are performed within 3 days before study drug dosing unless otherwise specified. Day 1 ophthalmology assessments (ie, CAS and proptosis measurement) and urine pregnancy test should be used to confirm eligibility before first dose is administered.

[redacted]

The study site's pharmacist (or pharmacist designee) will obtain the study drug assignment by IRT. A patient is considered randomized [redacted] when the pharmacist obtains the study drug assignment. Treatment assignments will be performed centrally by IRT.

6.4. For Randomized Treatment Arms: Blinding and Breaking Code

This study is a randomized, double-masked design. Bias is minimized by patient randomization and masking. The PI (or designee), study personnel, and patients should not make any effort to determine which study drug therapy is being received. Unmasked pharmacy personnel and unmasked study personnel (eg, unmasked Pharmacy Monitor, PK analyst, statistician) will be utilized in this study.

All study personnel, including the Sponsor, PI (or designee), and site personnel involved in study conduct, and patients will remain masked to study medication assignment until otherwise specified, with the exceptions of a Pharmacy Monitor to monitor drug preparation and drug accountability during the study; cases in which unmasking is required due to a safety or tolerability issue; by designated unmasked study team members, as needed, to prepare analyses

in preparation for SRC meetings; or as requested by the SRC from the unmasked biostatistician if needed.

To maintain study masking, study drug preparation will be performed by an unmasked site pharmacist (or qualified unmasked personnel at the study site not involved with study procedures or evaluations) in accordance with the procedures outlined in the Pharmacy Manual.

Only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of a specific patient (eg, an AE to be of such severity as to require immediate specific knowledge of the treatment assignment), may the PI (or designee) obtain a patient's treatment assignment. All unmasking events must be reported to the Sponsor and Medical Monitor promptly. Prior to any unmasking, the PI (or designee) is strongly advised to discuss options with the Medical Monitor or appropriate Sponsor study personnel. As soon as possible and without revealing the patient's study treatment assignment (unless important to the safety of patients remaining in the study), the PI (or designee) must notify the Sponsor if the mask is broken for any reason and the PI (or designee) was unable to contact the Sponsor before unmasking. The PI (or designee) will record the date and reason for revealing the masked treatment assignment for that patient and the names and roles of the personnel unmasked in the source documentation.

Unmasked data may be reviewed by designated Sponsor personnel who are not responsible for study management or decisions that impact data integrity, in accordance with relevant study plans.

6.5. Dose Timing Adjustment after a Missed Dose of Study Drug

After a missed dose of study drug (ie, dosing not within the specified window allowed), the individual patient should be dosed as soon as possible. If study drug dosing is delayed by >1 week, it must be approved by the Medical Monitor and subsequent study visits (ie, study assessments and study drug dosing) of the patient may be adjusted accordingly in order to maintain the planned timing interval between doses. Any additional or alternative changes to the timing of individual study visits, assessments, and/or study drug dosing after a missed dose of study drug are allowed if approved by the Medical Monitor.

6.6. Study Intervention Compliance

Treatment compliance will be documented in the eCRF by recording the date, start time, and if the dose of study drug was completely infused.

6.7. Treatment of Overdose

There is no specific antidote for overdose with LASN01. In the event of a suspected overdose, contact the Medical Monitor and institute appropriate supportive clinical care, as dictated by the patient's clinical status.

6.8. Prior and Concomitant Medications, Substances, and Therapy

6.8.1. Previous Medications, Substances, and Therapy

Patients with previous use of the following medications, substances, and therapy will be excluded from the study.

- Medical treatment for TED (Inclusion Criterion #5, Section 5.1), with the exception of:
  - Local supportive measures
  - Mycophenolate, and oral or injectable steroids if the maximum cumulative dose is ≤4.5 g methylprednisolone or equivalent with ≥6 weeks between last administration of oral steroids and/or mycophenolate and Screening
  - Previous use of rituximab, tocilizumab, or any monoclonal antibody for immunomodulation, more than 9 months before Day 1
  - Previous use of any other immunomodulating therapy more than 3 months before Day 1 unless approved by the Medical Monitor
- Use of oral and/or IV corticosteroid for conditions other than TED in the 6 weeks before Day 1 (topical steroids for conditions other than TED are allowed) (Exclusion Criterion #6, Section 5.2)
- Any investigational therapy, cytotoxic, immunosuppressive, or cytokine modulating therapies, or any therapy that, in the opinion of the PI, may compromise the objectives of the study (Exclusion Criterion #17, Section 5.2) within 4 weeks or 5 half-lives (whichever is greater) before Screening.
- Previous use of an anti-IGF-1R targeted treatment at any time [redacted] (Exclusion Criterion #9, Section 5.2)
- Use of selenium within 3 weeks before Day 1 (multivitamins that include selenium are allowed in usual doses) (Exclusion Criterion #10, Section 5.2)
- Use of biotin (including multivitamins that include biotin) within 2 days before any laboratory collection (Exclusion Criterion #11, Section 5.2)
- Previous surgery in the study eye, with the exception of routine or minor procedures at least 3 months before Screening as determined by the PI or designee (Inclusion Criterion #5, Section 5.1)
- Orbital irradiation/radiotherapy (Inclusion Criterion #5, Section 5.1)
- Orbital surgery (Inclusion Criterion #5, Section 5.1)
- Use of an IV anti-infective agent to treat an infection within 4 weeks prior to Day 1 (Exclusion Criterion #19, Section 5.2)

6.8.2. Concomitant Medications, Substances, and Therapy

Use of the following concomitant medications, substances, and therapies during the study until the EOS visit is prohibited. EXCEPTIONS: any medications that are needed as treatment for AEs are allowed as determined by the PI. In such cases, the PI and the Medical Monitor will determine whether the patient may continue in the study.

- Corticosteroids (oral or IV); if clinically indicated for conditions other than TED, the PI (or designee) should discuss with the Medical Monitor
- Rituximab, tocilizumab, teprotumumab, or any monoclonal antibody for immunomodulation
- Other immunomodulating therapy (unless approved by the Medical Monitor)
- Biotin (including multivitamins that include biotin) within 2 days before any laboratory collection
- Selenium

  EXCEPTION: Multivitamins that include selenium are allowed in usual doses
- Orbital irradiation/radiotherapy or planned orbital surgery for TED
- Vasoconstrictive eye drops and any eye drops (eg prostaglandin analogs) that can cause eye redness and swelling that impact the interpretation of study results are not permitted during the study; the use of other eye drops may be permitted if approved by the Medical Monitor. Artificial tears for dry eyes are permitted.

Note: Local supportive measures for TED, simple analgesics (eg, acetaminophen, non-steroidal anti-inflammatory therapies), and non-steroidal medications/supplements for conditions other than TED (eg, topical corticosteroids) are permitted during the study.

The following prior and concomitant medications are acceptable:

- Stable doses of thyroid replacement
- Medications for the treatment of hyperthyroidism
- Stable doses of oral contraceptive therapy are permissible
- Killed and inactive vaccines, including mRNA vaccines (eg, pneumonia, influenza, SARS-CoV-2) and live attenuated vaccines (eg, varicella) are permitted

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Stopping Rules

Study drug must be discontinued in any individual patient who experiences a study drug-related SAE or any other AE that, in the opinion of the PI, warrants discontinuation of study drug. Before discontinuation, please discuss with the Medical Monitor.

7.2. Early Discontinuation of Study Intervention

Patients who prematurely discontinue study drug should still remain on study for scheduled visits and assessments and every effort should be made to obtain all protocol-specified assessments to avoid losing data that is needed to evaluate safety and efficacy. The assessments for primary, secondary, and exploratory endpoints, including the MRI and facial photography, should be completed within 30 days of the study drug discontinuation. The reason for premature discontinuation of study drug administration should be recorded on the appropriate page(s) of the eCRF.

Study drug must be discontinued in case of progressing disease posing an unacceptable risk to the patient that requires immediate treatment. In such cases, the PI should contact the Sponsor and the PI and the Sponsor Medical Monitor will discuss and determine whether the patient should continue in the study.

Reasons for withdrawal from study drug may include, but are not limited to:

- Withdrawal of consent
- An AE, which, in the opinion of the PI (or designee), warrants the patient's discontinuation of study drug infusion; in the event of study drug withdrawal due to the occurrence of an AE, the Medical Monitor must be notified within 24 hours
- Non-compliance with study drug administration or other protocol procedures
- Prohibited concomitant medication
- Physician decision
- Pregnancy
- Study termination

A patient who is withdrawn from study drug, or patients who are randomized, but not dosed, for reasons not related to study drug or progression of TED may be replaced at the discretion of the Sponsor.

7.3. Participant Discontinuation/Withdrawal from the Study

Patients who wish to withdraw completely from this clinical study should be encouraged to complete the EOS/ET visit. However, patients may withdraw consent to participate in this study at any time without penalty or loss of benefits to which the patient is otherwise entitled. Every reasonable effort should be made to determine the reason a patient withdraws prematurely, and

this information should be recorded on the appropriate page(s) of the eCRF. Patients may be withdrawn from the study for any of the following reasons:

- Withdrawal of consent
- Protocol non-compliance with protocol procedures
- Lost-to-follow-up
- Physician decision
- Study termination

7.4. Criteria for Discontinuation of Study

In the event of a negative change to the risk/benefit assessment, study enrollment will be suspended and the protocol revised as needed to ensure patient safety. Enrollment will be suspended if ANY of the criteria listed below are met. If the study is suspended due to meeting any of the criteria below, it may only be restarted after review and agreement by SRC and Sponsor. In countries for which restart of enrollment is considered a substantial amendment, enrollment will only be restarted once the relevant health authorities approve the revised protocol.

- The occurrence of an SAE or severe AE, assessed as related to the study drug, of similar origin in ≥3 patients
- If unacceptable risks to study patients are identified
- If, in the Sponsor's judgment, there are no further benefits to be achieved from the study

In the event that the clinical development of the study drug is discontinued, the Sponsor shall inform the PI/institution and regulatory authorities.

8. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study-related procedures, the PI (or designee) will obtain written informed consent from patients.

Planned timepoints for all safety assessments are provided in the Schedule of Activities (Section 1.3). Study procedures should be completed within the windows provided in the Schedule of Assessments and Procedures. However, if a patient is unable to attend a visit within the specified window, the PI (or designee) should discuss appropriate scheduling with the Medical Monitor.

For this study, the blood sample for LASN01 PK is a key parameter and any time point after start of infusion for blood sample needs to be collected within the specified window. All other procedures should be completed as close to the prescribed/scheduled time as possible. Unscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

No genotyping or DNA "profiling" will be performed on any collected samples.

8.1. Efficacy Assessments

During determination of eligibility for the study, the more severely affected eye will be defined as the study eye by the PI or designee. This will be based on the severity of proptosis in both eyes at Day 1. If both eyes are affected equally, the PI or designee will select the study eye and may take into account other factors such as the CAS. Both eyes will be assessed for efficacy and safety at designated study visits, but the study eye will be used to assess the primary clinical end point. If only one eye is determined to meet the eligibility criteria, that is the study eye by default.

The same assessor should conduct the TED related ophthalmic assessments at each study visit. This includes assessment of proptosis, CAS, conjunctival redness, chemosis, lid swelling, lid aperture, diplopia and duction testing for extraocular movements. If a different assessor than the initial/main assessor performs these assessments at a particular visit due to schedules, etc., then these assessments should be repeated by the initial/main assessor as soon as possible.

The following thyroid eye disease assessments will be further detailed in a study manual provided to the sites.

8.1.1. Proptosis

Assess degree of proptosis and reduction from Baseline in proptosis in the study eye and fellow eye using a Hertel Exophthalmometer. The same instrument and assessor should be used for all assessments. Instructions will be provided in a study manual.

8.1.2. CAS Assessments

CAS assessments are presented in Table 4. The same assessor should conduct each CAS evaluation at each visit for the full duration of the study. CAS assessment should be completed prior to any eyes drops administered for dilation or any other purpose.

Table 4. CAS 7-point Scale

Item [a]	Description	7-point CAS
1	Spontaneous orbital pain.	
2	Gaze evoked orbital pain.	
3	Eyelid swelling that is considered to be due to active (inflammatory phase) TED	
4	Eyelid erythema	
5	Conjunctival redness that is considered to be due to active (inflammatory phase) TED (ignore "equivocal" redness)	
6	Chemosis	
7	Inflammation of caruncle or plica	
	Total 7-point CAS	**Add items 1-7**

CAS = clinical activity score; TED = thyroid eye disease
a Each item is scored (1=present; 0=absent), and scores for each item are summed for total score.

8.1.2.1. Spontaneous Orbital Pain and Gaze Evoked Orbital Pain

Spontaneous orbital pain and gaze evoked orbital pain assessments will use the Numerical Rating Scale. The patient is asked to indicate the value of her/his pain on the scale for the right eye and the left eye. An 11-point scale is used with "0" representing "no pain" and "10" representing the "most severe pain imaginable" in the past 4 weeks. The patient verbally picks the number that best describes the pain intensity. Document the patient's pain score in the source documentation. For gaze evoked orbital pain the patient will be asked about orbital pain that occurs on eye movement in any direction of gaze.

The same assessor should conduct the evaluation at each visit for the full duration of the study. Instructions will be provided in a study manual.

8.1.2.2. Conjunctival Redness

Conjunctival redness will be graded from 0 to 3. This is a clinical assessment to evaluate the severity of redness. For the overall CAS assessment, Grade 0 and 1 are considered absent (and should receive a score of '0' in the CAS scoring) and Grade 2 or 3 are considered present (and should receive a score of 1 in the CAS scoring).

Grade 0 – none

Grade 1 – mild: equivocal redness

Grade 2 – moderate: defined redness, <50% redness excluding plica and caruncle

Grade 3 – severe: >50% redness excluding plica and caruncle

The same assessor should conduct the evaluation at each visit for the full duration of the study. Instructions will be provided in a study manual.

8.1.2.3. Eyelid Swelling

Eyelid swelling will be graded from 0 to 3. This is a clinical assessment to evaluate the severity of lid swelling. For the overall CAS assessment, Grade 0 and Grade 1 below are considered absent (and should receive a score of '0' in the CAS scoring) and Grade 2 and 3 are considered present (and should receive a score of "1" in the CAS scoring).

Grade 0 – none

Grade 1 – swelling very superficial, changed appearance like thickened skin

Grade 2 – definite swelling but no lower eyelid festoons, and in the upper eyelid, the skin fold becomes angled fold on 45º downgaze

Grade 3 – lower eyelid festoons or upper lid fold remains rounded on 45º downgaze

The same assessor should conduct the evaluation at each visit for the full duration of the study. Instructions will be provided in a study manual.

8.1.2.4. Chemosis

Chemosis will be graded from 0 to 3. This is a clinical assessment to evaluate the severity of chemosis. For the overall CAS assessment, Grade 0 is considered absent (and should receive a score of '0' in the CAS scoring) and Grade 1, 2 or 3 are considered present (and should receive a score of 1 in the CAS scoring).

Grade 0 – None

Grade 1 – Conjunctiva looks pale and loses transparency

Grade 2 – Bulging of conjunctiva

Grade 3 – Chemosis prevents appropriate palpebral closure

The same assessor should conduct the evaluation at each visit for the full duration of the study. Instructions will be provided in a study manual

8.1.3. Lid Aperture

Distance between the lid margins in mm with the patient looking in the primary position, sitting relaxed and with distant fixation. Margin reflex distance 1 (MRD1) and MRD2 parameters will be measured. The same assessor should conduct the evaluation at each visit for the full duration of the study. Instructions will be provided in a study manual.

8.1.4. Lagophthalmos, Eyelid Retraction, and Von Graefe's Sign

Presence or absence of lagophthalmos and Von Graefe's sign will be recorded.

Eyelid retraction is a displacement of the upper eyelid superiorly or lower eyelid inferiorly.

Instructions will be provided in a study manual.

8.1.5. Assessment of Diplopia and Extraocular Movements

Bahn-Gorman Scale for Diplopia

- Grade 0 – Normal
- Grade I – Intermittent diplopia: present only when patient is fatigued
- Grade II – Inconstant diplopia: present only on lateral or upward gaze
- Grade III – Constant diplopia: present on straight and level gaze and correctable with prisms
- Grade IV – Constant diplopia: present on straight and level gaze but not correctable with prisms

Duction Testing for Extraocular Movements

- Assessment of extraocular movements in all 4 primary directions (up, down, nasal and temporal) will be performed.

The same assessor should conduct the evaluation at each visit for the full duration of the study. Instructions will be provided in a study manual.

8.1.6. Orbital MRI

Axial high-resolution images will be obtained locally and transmitted to a central radiology vendor for review. Besides assessment of proptosis, the orbital MRI sequences may provide (but not limited to) volumetric analysis of eye compartments such as muscle and fat, and assessment of inflammation in the orbit as well as any damage to the optic nerve. Further instructions will be provided in a study manual. Patients who cannot have an MRI due to the presence of metal or other known reason may participate in the study without having the MRI scans. In the US only, an orbital CT scan may be performed if the patient cannot have an MRI scan.

8.1.7. Facial Digital Photographs

External photographs of the eyes that capture at minimum the five cardinal positions of gaze (up, down, right, left and primary gaze) may be taken at the study sites and transmitted to a central reading vendor for review. The study will only use the 5 cardinal directions of gaze for evaluation. The whiteness of the sclera, MRD1, MRD2, and eye movement will be assessed from the digital photographs to confirm the clinical assessment including CAS, lid retraction, and eye movement measurements. Further instructions will be provided in a study manual.

8.2. Safety Assessments

An SRC will be formed for periodic reviews of safety and available PK and PD data. For the randomized, double-blind treatment arms, the SRC will review masked data. The SRC will be minimally composed of the Medical Monitor, at least 1 study PI, and at least 1 independent member with expertise in the treatment of TED. In cases where the SRC determines that an unexpected or critical finding requires expert opinion or access to unmasked data, the SRC may refer the question to at least 3 independent experts selected by the Sponsor, including the SRC

Chair, to assess the situation by reviewing necessary unmasked data and provide recommendation back to the SRC. The SRC charter will describe the committee member structure and details for the conduct and safety review meetings.

Safety will be assessed throughout the study by examination of visual acuity, visual fields, and color defects; TEAEs; changes in concomitant medications; and changes from Baseline in clinical laboratory evaluations, vital signs, 12-lead ECGs, ophthalmic assessments, and physical examinations. Safety assessments by visit are listed in Table 1. Safety monitoring (Section 10.1.6.1) and reporting (Section 8.3) are summarized. Additional safety assessments may occur at the discretion of the PI (or designee).

Any ongoing study drug-related SAEs or severe TEAEs present at the time of study termination will be followed until resolved or until the event stabilizes and the overall clinical outcome has been ascertained. All other TEAEs considered related to study drug and SAEs considered not related to study drug will be followed for 30 days after the EOS/ET visit or after the last dose of study drug, whichever is later.

In the event of unexplained, treatment-emergent, clinically significant, abnormal laboratory values or clinically significant changes in laboratory values from Baseline, the laboratory tests should be repeated immediately and followed until the values have returned to within the reference range or to Baseline.

8.2.1. Best Corrected Visual Acuity, Visual Fields, and Color Defects

Change of best corrected visual acuity by ≥3 lines (15 words) at 4m on the ETDRS chart, new or increased visual field (by Humphrey field testing) or color defects (Ishihara test) may require additional assessments. If a different measure or assessment is used, it must be approved by the Medical Monitor and equivalent criteria used for assessment. Instructions will be provided in a study manual.

8.2.2. Slit Lamp Biomicroscopy and Intraocular Pressure

Slit lamp biomicroscopy and intraocular pressure (IOP) should be performed with each ophthalmic exam.

8.2.3. Dilated Fundoscopy

Dilated fundus exam will be assessed by the fundus ophthalmoscopy after dilation of the right eye and the left eye.

8.2.4. Physical Examinations

Complete physical examination includes general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes.

Brief examinations are limited, symptom-directed, physical examinations as clinically indicated.

8.2.5. Body Weight

The study site staff should use a digital precision scale if possible and record the weight in kilograms or pounds to the first decimal point (eg, 95.3 kg). The same scale should be used, and the patient should wear a standard hospital-type gown or equivalent light clothing and no shoes for the body weight measurement.

8.2.6. Vital Signs

Vital sign measurements in this study will include seated respiratory rate, blood pressure, pulse rate, and body temperature. Vital signs should be measured after the patient rests for approximately 5 minutes in a sitting position. If infusion-associated events occur during the infusion, vital signs will be checked every 5 minutes until stable, then every 15 minutes for two more checks. Additionally, vital signs will be monitored every 15 minutes from the start of the infusion until 60 minutes after its completion for any subsequent infusions following previous immediate or delayed infusion-associated events.

8.2.7. ECGs

Perform triplicate ECGs within a 15-minute period, separated by ≥1 minute. ECG recordings will be taken after ≥5 minutes in a semi-supine, quiet-rest position (head of bed between 0° and 90°), and before obtaining any blood sample.

The results of all 12-lead ECGs (heart rate, QTcF, PR interval, RR interval, QRS interval) will be recorded to the eCRF.

If the 12-lead ECG must be performed with the patient in another position (eg, sitting, standing), the PI (or designee) should record the alternative position. The PI (or designee) should date and sign the ECG tracing and record the clinical significance of any abnormal result on the tracing. ECGs will be interpreted by a qualified physician (the PI or designee).

8.2.8. Clinical Safety Laboratory Tests

Procedures for obtaining, processing, shipping, and handling laboratory specimens will be detailed in the Laboratory Manual.

Clinical laboratory tests include chemistry, hematology, coagulation, UA, urine drug screen, and additional tests listed in Appendix 2, Section 10.2.

The PI (or designee) will evaluate all Screening and safety laboratory reports and will sign and date the review. Any out-of-range laboratory results should be assessed for clinical significance. The PI (or designee) should follow all clinically significant laboratory abnormalities occurring during the study that were not present at Baseline as needed. These abnormalities should be evaluated with additional tests, if necessary, until the underlying cause is diagnosed, event becomes stable or resolution occurs. The diagnosis and resolution date must be reported to the Sponsor via the eCRF.

8.2.9. Pregnancy Testing

WOCBP must have a negative serum pregnancy test at Screening, a negative urine pregnancy test on Day 1, and be willing to undergo additional pregnancy tests, as required, throughout the study. WOCBP will have urine pregnancy tests predose on dosing days and a serum pregnancy test at the EOS/ET visit.

Serum FSH levels will be tested in women at Screening and must be in the menopausal range to confirm postmenopausal status.

8.3. AEs, SAEs, and Other Safety Reporting

The definitions of AEs and SAEs are provided in Appendix 3, Section 10.3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

Detection and recording of AEs and SAEs starts from the signing of the ICF until the Day 365/Week 53 visit. From this visit to the EOS visit, only treatment-related AEs/SAEs will be recorded. AEs that occur after signing the ICF, but before the first dose of study drug, will be recorded to the eCRF as medical history, unless related to a study procedure. Detection and recording of TEAEs will start at the time of the first dose of study drug. Any SAE that occurs after signing the ICF (before or after the first dose of study drug) will be recorded to the eCRF as an SAE.

8.3.2. Method of Detecting AEs and SAEs

The PI (or designee) is responsible for detection, recording, and reporting of events that meet the criteria and definition of an AE (Appendix 3, Section 10.3).

8.3.3. Follow-Up of AEs and SAEs

Following initial observation of an AE/SAE, the PI (or designee) is required to proactively follow progress of the relevant event (Section 10.3.3.4).

8.3.4. Pregnancy

If a patient's pregnancy test is positive at Screening or Day 1, she will be referred to her primary care provider for follow-up and will not be included in the study.

Patients must be instructed to inform the PI (or designee) *immediately* if they (for female patients) or their partner (for male patients) become pregnant during the study or for 90 days after the last dose of study drug or until the EOS/ET visit, whichever is later. In the event of a confirmed pregnancy, the following actions should be taken:

- Study drug should be discontinued immediately
- The pregnancy should be reported to the Medical Monitor within 24 hours of notification using the applicable Pregnancy Report Form

- The PI (or designee) should counsel the patient regarding the possible effects of prior LASN01 exposure on the fetus and the need to inform the study site of the outcome of the pregnancy
- The patient must be monitored until the immediate postnatal period or until termination of the pregnancy. The outcome should be reported using the Pregnancy Report Form.

Pregnancy is not an AE, in and of itself. However, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. A spontaneous abortion is always considered an SAE and will be reported as described in the AE and SAE sections (Section 10.3.1 and Section 10.3.2). Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to the Medical Monitor.

8.3.5. AESIs

No AESIs have been identified with LASN01 based on preclinical metabolic and toxicity studies and the Phase 1/2a study (LASN01-CL-1101).

8.4. PK Assessments

Procedures for collection, storage, and shipping of PK samples are described in the Laboratory Manual. Blood (serum) samples from all patients who receive ≥1 complete dose of LASN01 will be analyzed by a validated enzyme-linked immunosorbent assay method for the concentration of LASN01. The serum PK parameters of LASN01 will be determined based upon the LASN01 concentrations and actual time of PK sample collection relative to the previous dose.

8.5. PD and Biomarker Assessments

Blood draws will be collected for exploratory assessments of circulating protein biomarkers relevant to the IL-11 pathway in TED, fibrosis, and inflammation. Procedures for collection, storage, and shipping of PD and biomarker assessments are described in the Laboratory Manual.

8.6. Immunogenicity Assessments

Immunogenicity will be determined by assessment of ADA levels. Procedures for collection, storage, and shipping of samples for ADA assessments are described in the Laboratory Manual.

8.7. Retention of Samples

Samples may be retained for a maximum of 15 years after study completion at a storage facility before destruction. The retention period enables the use of new technologies, responses to regulatory authorities, and investigation of variable responses that may not be apparent until later in the development of LASN01 or after LASN01 is commercially available.

Samples will not be used to conduct unspecified disease or population genetic research.

9. STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be approved prior to database lock and will include a comprehensive description of the statistical analysis details described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Analysis Sets

Analysis populations are:

- Efficacy Population: all randomized patients who received at least 1 dose of study medication and 1 post-dose primary efficacy assessment, with treatment assignment designated according to randomized treatment.
  - [redacted]
- Per-Protocol Population: includes all patients in the Efficacy Analysis Population who complete the treatment and the primary efficacy analysis and do not incur any major protocol violation that would challenge the validity of their data, as defined in the SAP
- Safety Population: all randomized patients who receive ≥1 dose of study drug
  - [redacted]
- PK Analysis Population: all patients who receive ≥1 complete dose of study drug and for which ≥1 valid PK parameter can be calculated
- PD Analysis Population: all patients who receive ≥1 complete dose of study drug and who have ≥1 post-therapy PD assessment

9.2. Statistical Analyses

9.2.1. General Considerations

An SRC will be formed for periodic reviews of safety and available PK and PD data. The SRC will be minimally composed of the Medical Monitor, at least 1 study PI, and at least 1 independent member with expertise in the treatment of TED. In cases where the SC determines that an unexpected or critical finding requires expert opinion or access to unmasked data, the SRC may refer the question to at least 3 independent experts selected by the Sponsor, including the SRC Chair, to assess the situation by reviewing necessary unmasked data and provide recommendation back to the SRC. The SRC Charter will describe the committee member structure and details for the conduct and safety review meetings.

Unmasked data may be reviewed by designated Sponsor personnel who are not responsible for study management or decisions that impact data integrity, in accordance with relevant study plans, including for interim analysis.

A SAP will be prepared and finalized before database lock and analysis of data. Any deviations from the final SAP will be described and justified in the study report.

Data will be summarized and listed separately. Continuous data will be summarized using the number of patients, mean, standard deviation, median, minimum, and maximum values for continuous variables, whilst categorical data will present the numbers and percentages of patients within each category. Listings of individual patient data will also be produced.

[redacted]

Baseline will be defined as the last available, non-missing observation before the first study drug administration. In general, "Unknown", "Not Done", "Not Applicable", and other classifications of missing data will not be considered when calculating Baseline observations. However, valid categorical observations will be considered for Baseline calculations. In addition, non-missing results from unscheduled assessments before the first study drug administration may also be considered in the calculation of Baseline observations.

9.2.2. Analysis of Study Population and Patient Characteristics

Patient disposition, including the number of patients dosed and number of patients completing the study, will be summarized. Patient disposition and demographics (including age, race, ethnicity, gender, height, weight, and BMI at Screening) and baseline characteristics will be summarized for the Safety Population.

9.2.3. Efficacy Analysis

Efficacy will be assessed using the Efficacy Analysis Population. However, any or all of these analyses may also be performed in the Per-Protocol Analysis Population as exploratory analysis.

[redacted]

9.2.3.1. Efficacy Analysis for the Randomized Treatment Arms

The primary clinical endpoint analysis is the percentage of patients in the randomized treatment arms who have received LASN01 (pooled analysis of 300 and 600 mg Q4W) showing a response in proptosis (≥2 mm decrease from Baseline) in the study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye at Week 37 compared with placebo.

The primary endpoint will be analyzed using a one-tailed Fisher's exact test at an alpha of 0.10 and will report the percentage of LASN01 (300 mg and 600 mg Q4W pooled) responders compared to placebo responders at the Week 37 timepoint. Results, including p-values, will be summarized and presented in contingency table. 95% confidence intervals will be reported.

9.2.4. Sensitivity Analysis for Primary Endpoint Using MMRM

This analysis will be conducted using an MMRM model. The model will incorporate fixed effects for treatment group, baseline proptosis, and visit (Week 37). An unstructured covariance matrix will be used to model the repeated measures. Missing data will be handled under the Missing At Random (MAR) assumption. Additionally, alternative covariance structures (e.g.,

compound symmetry) and covariate adjustments (e.g., age, sex) will be evaluated to test the stability of the treatment effect estimates.

The treatment effect will be estimated by examining the fixed effect of LASN01 versus placebo at Week 37. Model comparisons will be conducted to ensure consistency across different covariance structures and covariate adjustments. Results will include estimated treatment differences with 95% confidence intervals. Results will be summarized and presented in a table for comparison with the primary analysis of the primary endpoint.

Secondary endpoint analyses related to efficacy in the randomized treatment arms include:

- Percentage of patients who have received LASN01 (600 mg Q4W) showing a response in proptosis (≥2 mm decrease from Baseline) in the study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73 following treatment with IV LASN01 compared with placebo
- Percentage of patients who have received LASN01 (300 mg Q4W) showing a response in proptosis (≥2 mm decrease from Baseline) in the study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73 following treatment with IV LASN01 compared with placebo
- Percentage of patients who have received LASN01 (pooled analysis of 300 and 600 mg Q4W) showing a response in proptosis (≥2 mm decrease from Baseline) in the study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye at Weeks 17, 21, 25, 29, 33, 41, 45 57, 65, and 73 following treatment with IV LASN01 compared with placebo.
- Mean change from Baseline in proptosis in patients who have received LASN01 (600 mg Q4W) compared with placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73
- Mean change from Baseline in proptosis in patients who have received LASN01 (300 mg Q4W) compared with placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73
- Change in CAS from Baseline on a 7-point scale for pooled LASN01 and each LASN01 dose group versus placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73
- Change in lid retraction from Baseline (in mm) for pooled LASN01 and each LASN01 dose group versus placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73
- Change in lid aperture from Baseline (in mm) for pooled LASN01 and each LASN01 dose group versus placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73
- Percentage of patients with lagophthalmos for pooled LASN01 and each LASN01 dose group versus placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73
- Percentage of patients with Von Graefe's sign for pooled LASN01 and each LASN01 dose group versus placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73
- Change in subjective diplopia by the Bahn-Gorman scale for pooled LASN01 and each LASN01 dose group versus placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73

- Change in extraocular movements (4 Quadrants, in degrees) from Baseline for pooled LASN01 and each LASN01 dose group versus placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73

Exploratory endpoint analyses related to efficacy include:

- Changes in exploratory MRI imaging parameters from Baseline for pooled LASN01 and each LASN01 dose group compared with placebo at Weeks 9, 13, 29, 41, 53, and 73
- Facial imaging of the eye assessing mean values, change from earliest timepoint collected, and change from baseline (when available) in conjunctival redness, MRD1 and MRD2, and eye movement at Week 9, 13, 17, 21, 25, 29, 37, 45, 53, and 73
- Responder analyses assessing TED- related clinical parameters in either eye.

[redacted]

9.2.5. Safety Analyses

Safety will be assessed in the Safety Analysis Population.

Safety will be evaluated by presenting listings and summaries of AEs, vital signs, 12-lead ECGs, ophthalmic assessments, conventional clinical laboratory evaluations (serum chemistry, hematology, coagulation, and UA evaluations), prior and concomitant medication use, treatment compliance, and exposure. Safety variables will be tabulated by treatment arm, LASN01 dose level and placebo. Other safety measures (eg, physical examination findings, pregnancy test results, drug screening test results) will be listed.

AEs will be coded using the MedDRA version 24.1 or higher. The incidences of TEAEs will be presented by system organ class and preferred term according to MedDRA, by relationship to the study drug, by severity, and by whether or not they resulted in alteration of administration of or discontinuation of study drug. A TEAE is defined as an AE that occurs during or after the first study drug infusion. A TRAE is defined as an AE with a plausible temporal relationship between the onset of the AE and administration of study drug (and as further defined in Table 6). TEAEs will be captured until Day 365/Week 53. From this visit to the EOS visit, only TRAEs will be recorded. In addition, the incidences of serious TEAEs and TEAEs leading to discontinuation of study drug will be presented by system organ class, preferred term, and relationship to study drug.

Descriptive statistics and change from Baseline for clinical laboratory test and vital sign results will be presented by scheduled time point. Incidences of potentially clinically significant clinical laboratory results, determined based on normal ranges, will also be summarized by scheduled time point. The numbers and percentages of abnormal 12-lead ECGs will be provided by scheduled time point.

9.2.6. PK Analyses

PK will be assessed in the PK Analysis Population.

Blood (serum) samples from all patients who received ≥1 complete dose of LASN01 will be analyzed for the concentration of LASN01 by a validated enzyme-linked immunosorbent assay method in the PK Analysis Population. Serum concentration-time profiles will be constructed for each patient and each LASN01 dose level. At a minimum, for each serum concentration-time curve, the following PK parameters will be determined directly from inspection of the data or will be calculated using non-compartmental methods with validated PK software:

At a minimum, the following PK parameters will be calculated:

- C_{max}
- T_{max}
- $AUC_{0\text{-}last}$
- $AUC_{0\text{-}28d}$

The following parameters will be calculated as feasible given the observed serum concentration-time data:

- $AUC_{0\text{-}\infty}$ (first dose only)
- CL
- V_z
- V_{ss}
- λz
- $t_{1/2}$

Summary statistics (N, mean, standard deviation, coefficient of variation, median, minimum, and maximum) will be tabulated by LASN01 dose level for serum concentrations at each nominal time and for the PK parameters. Geometric means and geometric coefficient of variations will also be presented for all PK parameters with the exception of T_{max}. Linear and log-linear plots will be created to display mean (by dose level with and without standard deviation) and individual concentration-time profiles. Statistical analysis will be performed to assess dose proportionality, and additional details will be provided in the SAP.

9.2.7. Participant Study Withdrawal and Premature Termination of Study Drug

Enrollment and withdrawals from the study and from study drug will be summarized by LASN01 treatment arm, dose level and placebo.

9.2.8. Deviation Reporting

Protocol deviations are defined as any variation from the protocol, including enrollment of a patient who did not meet all inclusion and exclusion criteria and failure to perform the assessments and procedures within the required time frames.

9.3. Handling of Dropouts and Missing, Unused, and Spurious Data

Every effort will be made to collect all data at specified times. No substitutions will be made for missing data, unless explicitly specified in the SAP.

9.4. Interim Analyses

Interim analyses may be performed when at least 50% of evaluable patients in the randomized treatment arms complete at least 8 weeks in the study (details will be provided in the SAP) to inform further development. The interim analysis may also include the open-label treatment arm.

9.5. Sample Size Determination

This study will enroll up to 36 evaluable patients with TED in 4 treatment arms. Approximately 24 patients will be randomized to LASN01 600 mg Q4W, LASN01 300 mg Q4W, or placebo treatment arms in a 1:1:1 ratio [redacted].

For the three randomized treatment arms: The pooled primary analysis represents an aggregate 2:1 randomization of LASN01:placebo with approximately 24 total patients. The success rate for placebo was assumed to be 15% (Teprotumumab – FDA Summary Basis of Approval 2020). Assuming a pooled success rate for LASN01 of 65% (ie, a pooled absolute treatment effect of 50% relative to placebo), the proposed sample size of 8 patients per treatment group gives approximately 81% power at the 10% level of statistical significance for a 1-sided Fisher's exact test of superiority of LASN01. If the placebo rate is 10% instead, the proposed sample size gives approximately 90% power at the 10% level of statistical significance. All calculations were performed using R Core Team (2022) Version 4.2.1. Power was determined using simulation methods with a simulation size of 10,000 and simulations were implemented using the 'statmod' package (Giner 2016).

[redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol, ICH Technical Requirements for Registration of Pharmaceuticals for Human Use E6: GCP Consolidated Guidelines, the ethical principles of the Declaration of Helsinki, the National Health and Medical Research Council Statement on Ethical Conduct in Human Research (2007, incorporating all updates as of July 2018), United States FDA GCP guidelines, and any additional regulatory authority and/or ethics committee required procedures.

10.1.2. Financial Disclosure

The financing and insurance for this study are outlined in the Clinical Trial Agreement.

10.1.3. Informed Consent Process

This study will be conducted in compliance with ICH E6(R2) GCP: Consolidated Guidelines pertaining to informed consent. Patients will give written consent to participate in the study at the first visit, prior to initiation of any study-related procedures, after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits. The ICF must be signed and dated by the patient prior to study participation. A copy of the ICF must be provided to the patient. If applicable, it will be provided in certified translation for non-English-speaking patients. Signed original ICFs must remain in the patient's study file and be available for verification by Sponsor at any time.

10.1.4. Regulatory Authority and Ethics Committee Approval

This protocol, the ICF, and all relevant supporting data must be submitted to the concerned regulatory authority and/or ethics committee for approval. The protocol, ICF, and any advertisement used to recruit study patients must be approved by the concerned regulatory authority and/or ethics committee. Approval of the protocol and ICF must be obtained by the concerned regulatory authority and/or ethics committee before the study may be initiated.

The PI (or designee) is responsible for informing the concerned ethics committee of the progress of the study, any changes made to the protocol, annual updates and/or request for reapproval, and when the study has been completed. The PI (or designee) is also responsible for notifying the concerned ethics committee of any significant AEs that occur during the study. The PI (or designee) may receive written safety reports or other safety-related communications from the Sponsor. The PI (or designee) is responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their ethics committee and archived in the site's study file.

10.1.5. Data Protection

Medical information obtained from patients during the course of this study is confidential and disclosure to third parties other than those noted (Section 10.1.7) is prohibited.

10.1.6. Data Quality Assurance

Training sessions, regular monitoring of PIs by Sponsor-designated personnel, instruction manuals, data verification, and cross checking will be performed to ensure quality of all study data. Investigator meetings will be held to prepare PIs and other study personnel for appropriate collection of study data.

Written SOPs will be followed to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Quality control will be applied to each stage of data handling.

The PI must make every effort to adhere to the protocol as detailed in this document and agree that the Sponsor must approve any change to the protocol before seeking approval from the concerned regulatory authority and/or ethics committee. The PI will be responsible for enrolling only those patients who have met all of the protocol inclusion criteria and none of the exclusion criteria.

10.1.6.1. Study Monitoring

Regular monitoring, as defined in ICH GCP, Section 1.8, “The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s)” will be conducted throughout the conduct of the study. Monitoring is an integral role in the quality control of a clinical trial and is designed to verify the quality of the study.

The purpose of monitoring is to verify that:

- Rights and well-being of the human patients are protected
- The reported study data are accurate, complete, and verifiable from source documents
- The conduct of the study is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements

An authorized Sponsor representative will conduct site visits to inspect study data, patients’ medical records, and eCRFs in accordance with ICH guidelines, GCP, and the foreign regulations and guidelines, as applicable. Both masked and unmasked monitors will be utilized for monitoring ongoing dose administration and protocol procedures.

The PI will allow representatives of the Sponsor and regulatory authorities to inspect facilities and records relevant to this study in a timely manner. It will be the responsibility of the PI to ensure that the essential documents are available at the PI or institutional site. Any or all of these documents may be pertinent to, and should be available for, monitoring by the Sponsor or inspection by the regulatory authorities as defined in the monitoring plan.

The Sponsor will review and validate study data as defined in the monitoring plan.

10.1.7. Source Documents

Source documents are defined as documentation related to original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, or study-specific email correspondence, computer printouts, laboratory evaluations, and recorded data from automated instruments. All source documents produced in this study will be maintained by the PI (or designee) and made available for inspections and monitoring by the Sponsor and by regulatory authorities. The original signed ICF for each participating patient shall be filed with records kept by the PI (or designee), and a copy shall be given to the patient.

The PI agrees by his/her participation that the results of this study may be used for submission to national or international registration. If required, these authorities will be provided with the name of the PI and his or her address, qualifications, and extent of involvement. It is understood that the PI (or designee) is required to provide Sponsor with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by any concerned regulatory authority and/or ethics committee, and the Sponsor, as appropriate.

10.1.8. eCRFs

The eCRF will be supplied by Sponsor or designee for the recording of all information and study data as specified by this protocol. All eCRFs must be completed by trained study personnel. The PI is responsible for ensuring that the eCRF data are entered and completed in a timely manner.

Once all data queries and issues have been resolved for each patient, the PI will electronically sign each patient's eCRF to attest to the accuracy of the data.

10.1.9. Retention of Records

Records and documents pertaining to the conduct of this study and the distribution of study records including eCRFs, ICFs, laboratory test results, safety reporting forms, source documents, medication inventory records, and adequate documentation of relevant correspondences (eg, letters, meeting minutes, telephone calls reports) must be kept on file by the PI for a minimum of 2 years after notification by the Sponsor that a marketing application has been approved for LASN01. If no application is filed or approved, these records must be kept for 3 years after the investigation has been discontinued and the United States FDA and applicable foreign authorities have been notified. The Sponsor will notify the PI of these events. No study records should be destroyed without prior authorization from the Sponsor.

10.1.10. Dissemination of Clinical Study Data

After the end of study, a CSR will be written and submitted to relevant IRB and regulatory authorities in accordance with local requirements.

At a patient's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

10.1.11. Study and Site Start and Closure

The Sponsor requires the following data and materials before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from Screening visit throughout the study until the EOS visit
- eCRFs (including data queries) properly completed by appropriate study personnel and signed and dated by the PI
- Copies of complete drug accountability records (drug inventory log and an inventory of returned or destroyed clinical material)
- Copies of protocol amendments and concerned regulatory authority and/or ethics committee approval and notification, if appropriate
- A summary of the study prepared by the PI (a summary letter is acceptable from the concerned regulatory authority and/or ethics committee)

10.1.11.1. Early Study or Site Termination

The study or study site may be terminated before study completion at the discretion of the Sponsor if any of the following criteria are met:

- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Administrative reasons, including, but not limited to, cancelation of IP development

Throughout the study, the PI is to make a reasonable effort to maintain the enrollment rate that was agreed upon with the Sponsor. The PI will also make a reasonable effort to enroll appropriate patients.

10.1.12. Publication Policy

This clinical study will be registered on https://clinicaltrials.gov/ or other registries by the Sponsor as required by local regulations, in keeping with the registration policy of the International Committee of Medical Journal Editors (2021).

Publication of study results may be addressed in the Clinical Trial Agreement. The Sponsor may publish the results of this study following completion of data analysis. The data generated in this clinical study are the exclusive property of the Sponsor and are confidential.

10.2. Appendix 2: Clinical Laboratory Tests

Hematology	Serum Chemistry	Urine Drug Screen
Hematocrit Hemoglobin Platelet count Red blood cell count Total and differential leukocyte count Reticulocyte count	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Bilirubin (total, indirect, and direct) Urea Calcium Creatine kinase Creatinine [b] Chloride Gamma glutamyl transferase Glucose Lactate dehydrogenase Potassium Sodium Total protein Hemoglobin A1c Thyroid stimulating hormone (TSH) Triiodothyronine (T3) Thyroxine (free T4) Thyroid stimulating immunoglobulin (TSI)	Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Methylenedioxymethamphetamine Methadone Opiates/opioids Phencyclidine Cotinine test
Urinalysis		**Additional Tests**
Appearance Bilirubin Blood [a] Color Glucose Ketones pH Protein [a] Leukocyte esterase Nitrite Specific gravity Urobilinogen [c]		Follicle-stimulating hormone as applicable Hepatitis B virus surface antigen Hepatitis C virus antibody Human immunodeficiency virus antibody (HIV-1 and HIV-2) Severe acute respiratory syndrome coronavirus 2 by PCR antibody test [c] Serum or urine pregnancy (for females of child-bearing potential only) [d]
Coagulation Tests		
Activated partial thromboplastin time Prothrombin time International normalized ratio		

a. If urinalysis is positive for protein or blood cells, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.
b. Creatinine clearance will be calculated using the Cockcroft-Gault formula.
c. To be conducted locally if applicable per the site's standard practice.
d. To be considered not of child-bearing potential, a female must either be surgically sterile for ≥6 months (ie, hysterectomy, bilateral salpingectomy, bilateral oophorectomy), or postmenopausal (no menses ≥12 months without an alternative medical cause and follicle-stimulating hormone in menopausal range).

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow Up, and Reporting

10.3.1. Definition of AE

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered study drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An AE can arise with any use of the study drug (eg, off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. The following are not AEs:

- Any non-serious AE that occurs after signing the ICF, but before dosing, unless related to a study procedure
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the PI (or designee) to be more severe than expected for the patient's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition)
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (eg, social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- Clinical changes consistent with progression of the underlying disease (ie, TED).

10.3.1.1. Definition of Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, ''reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

10.3.1.2. Definition of Life-Threatening AE or Life-Threatening Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ''life threatening'' if, in the view of either the PI (or designee) or Sponsor, its occurrence places the patient or patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

10.3.1.3. Definition of Unexpected AE or Unexpected Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘unexpected’’:

- If it is not listed in the IB or is not listed at the specificity or severity that has been observed, or
- If an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents.

‘‘Unexpected,’’ as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

10.3.2. Definition of SAE or Serious Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘serious’’ if, in the view of either the PI (or designee) or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE (Section 10.1.7)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect in the offspring of a patient who received study drug

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 patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.3.2.1. SAE Definition Clarifications

- Death is an outcome of an AE, and not an AE in itself
- All deaths during study drug infusion or occurring up to the EOS/ET visit, regardless of cause or relationship, must be reported
- “Occurring at any dose” does not imply that the patient is actively receiving study drug at the time of the event

- "Life-threatening" means that the patient was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, had it occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If an AE prolongs hospitalization, it is an SAE.
- "In-patient hospitalization" means the patient has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department (although an emergency department visit may define a medically important event, which is also considered an SAE).
- The PI (or designee) should attempt to establish a diagnosis of the event based on signs, symptoms, and other clinical information. In such cases, the diagnosis should be documented as the AE or SAE, rather than as the individual signs or symptoms.

10.3.3. Recording and Follow Up of AE and/or SAE

10.3.3.1. AE and SAE Recording

AEs that occur after signing the ICF, but before the first dose of study drug, will be recorded to the eCRF as medical history, unless related to a study procedure.

Any SAE that occurs after signing the ICF, but before the first dose of study drug, will be recorded to the eCRF as an SAE. The PI (or designee) will assess all AEs and SAEs and will record the following information on the appropriate eCRF:

- Date of onset
- Date of resolution or stabilization
- Severity
- Relationship to study drug
- Action taken with study medication

Events that, in the opinion of the PI (or designee), may represent intolerance of the IV infusion of study drug must be recorded as AEs on the eCRF. In general, these events will be temporally related to study drug infusion.

Laboratory abnormalities should not be recorded as AEs or SAEs unless they are associated with clinical signs or symptoms, require medical intervention or lead to interruption of study drug infusion or discontinuation. If the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than as the individual laboratory abnormality. In addition, laboratory abnormalities or other abnormal test assessments (eg, ECGs) that are associated with signs or symptoms must be recorded as AEs or SAEs if they meet the definition of an AE (or SAE) as described in Section 10.3.1 (or Section 10.3.2).

Additional details can be found in the applicable study plans.

10.3.3.2. Assessment of Intensity

All AEs will be graded for severity (Table 5).

The PI (or designee) will use the terms: Mild, Moderate, or Severe to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined in Table 5.

Table 5. Guidelines for Severity Assessments

CTCAE Criteria	Category	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Death	Death related to AE

CTCAE = Common Terminology Criteria for Adverse Events
Source = CTCAE V5 2017

10.3.3.3. Assessment of Causality

PI (or designee) should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly.

The following guidance should be taken into consideration (see also Table 6):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non−treatment-related factors that are known to be associated with the occurrence of the event

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is believed to be not related or unlikely related to study drug infusion, then an alternative explanation should be provided.

Table 6. Guidelines for Assessing Relationship of Event to Study Drug

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
Related	There is a plausible temporal relationship between the onset of the adverse event and administration of study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon rechallenge. An adverse event will be considered "Related", unless it fulfills the criteria specified for "Not Related".
Not Related	Evidence exists that the adverse event has an etiology other than the study drug (eg, preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (eg, cancer diagnosed 2 days after first dose of study drug).

10.3.3.4. Follow-Up of AEs and SAEs

The PI (or designee) should employ best medical judgment in determining how to manage AEs and SAEs. Any questions regarding AE or SAE management should be directed to the Medical Monitor.

Investigator Follow-Up

Any ongoing study drug-related SAEs or severe TEAEs present at the time of study termination for the patient (EOS visit or early termination) will be followed until resolved or until the event stabilizes and the overall clinical outcome has been ascertained or is not considered to be of clinical significance. All other TEAEs considered related to study drug and SAEs considered not related to study drug will be followed for up to 30 days after the later of the EOS/ET visit or the last dose of study drug. During the study period, resolution of AEs (with dates) should be documented on the AE eCRF and in the patient's medical record to facilitate source data verification. For the subjects who withdraw consent, the SAEs, severe TEAEs, and other TEAEs considered related to the study drug will be followed until the date of withdrawal of consent. The withdrawal of consent date will be recorded as the end date of the event.

Sponsor Follow-Up

For SAEs, AESIs, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (eg, from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case. For the subjects who withdraw consent these events will be followed until the date of withdrawal of consent. The withdrawal of consent date will be recorded as the end date of the event.

10.3.4. Reporting of SAEs

The Sponsor has requirements for expedited reporting of SAEs meeting specific criteria to regulatory authorities. Therefore, the Sponsor must be notified immediately regarding any SAE

that occurs after administration of the study drug and any SAE assessed by the PI (or designee) as related to a study procedure that occurs after the participant has signed an ICF.

All SAEs must be reported to the Medical Monitor within 24 hours of the Investigational Site's knowledge of the event. The study site will transmit a SAER using the designated safety mailbox.

An optional initial report can be made via telephone, but a completed SAER must still be faxed or emailed within 24 hours of the site's knowledge of the event. The Investigational Site will be provided with SAER forms wherein the following information is requested. In addition, relevant eCRF pages should be appended to communicate relevant study drug and patient outcome information.

- Patient identification number, PI name, and site number
- SAE information: event term, onset date, severity, and causal relationship
- The outcomes attributable to the event (eg, death, a life-threatening AE, inpatient hospitalization, prolongation of existing hospitalization, a persistent or significant disability or incapacity, or other important medical event[s])
- A summary of relevant test results, pertinent laboratory evaluations, and any other relevant medical history
- The first and last dates of study drug administration. NOTE: as this is a double-masked study, SAERs should not indicate specific study drug assignments
- Indicate if the study drug was discontinued or the study drug administration schedule modified
- Supplemental information may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates

The SAER should be faxed or emailed within 24 hours of the site's knowledge of the event with as much of the above information as available at the time. The following minimum information is required for reporting an SAE: patient identification, reporting source, and an event or outcome. Supplemental information may be transmitted using a FU report and should not delay the initial report. Supplemental information should be marked as a FU report and faxed or emailed using the safety mailbox. The Sponsor may contact the Investigational Site to solicit additional information or follow up on the event.

The PI (or designee) must take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the patient's eCRF. Withdrawal from the study and therapeutic measures taken shall be at the discretion of the PI (or designee). A full explanation for the discontinuation from the study should be made in the patient's medical records and the patient's eCRF.

All SAEs must be reported to the Investigational Site's concerned regulatory authority and/or ethics committee by the PI (or designee) in accordance with its regulations.

10.4. Appendix 4: Contraceptive Guidance

The risks of LASN01 administration during pregnancy have not been evaluated.

Female patients must be nonpregnant nonlactating, and either postmenopausal (ie, no menses for ≥12 months without an alternative medical cause and FSH level within the postmenopausal range), surgically sterile (ie, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) for ≥6 months, or agree to use a highly effective method of contraception from the start of the study and for ≥90 days following the last dose of study drug or until the EOS visit, whichever is later. Male patients must use a highly effective method of contraception unless considered permanently surgically sterile following a bilateral orchidectomy.

Highly effective methods of contraception are:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner (having received medical assessment of the surgical success)
- True sexual abstinence from the start of the study and for ≥90 days following the last dose of study drug or until the EOS visit, whichever is later, is acceptable only when refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, as described above. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea methods are not considered “true” abstinence and are not acceptable methods of contraception

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