TITLE PAGE

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

Sponsor:	**Lassen Therapeutics, Inc. (Lassen Therapeutics)** **5510 Morehouse Dr., Suite 100, City / State** **San Diego, CA 92121** **United States of America**
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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**
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Prepared by:	[redacted]

APPROVALS

This Statistical Analysis Plan was subjected to critical review and has been approved by the Sponsor and the following personnel:

APPROVALS			
If eSignature is used:	• *Attach eSig platform's audit log page and/or include a stamp that specifies the tool/platform used.* • *Use either a Date Field option or a Text Field to ensure the date is entered in dd-MMM-yyyy format.*		
Sponsor Representative by Signature: *(indicating this document has been reviewed and approved)*			
Name	**Title**	**Signature or eSignature**	**Date**
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APPROVALS			
Ora QC Review: *(indicating this document has been reviewed and approved)*			
Name	**Title**	**Signature or eSignature**	**Date**

[redacted]

DOCUMENT VERSION HISTORY

Document Version Number	Summary of Changes	Author Name	Document Version Date
1.0	Initial Release	[redacted]	19MAY2025
2.0	Either eye definition for responder analysis has been updated in Section 6. Section 16 has been updated to add either eye responder proptosis and total CAS, and either eye continuous total CAS analyses. Total CAS Figures have been added in Section 18.3 to align with the text in Section 11.2.1.	[redacted]	22MAY2025

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[redacted]

List of Abbreviations

Abbreviation	Definition
ADA	Anti-drug Antibodies
AE	Adverse Event
ANCOVA	Analysis of Covariance
$AUC_{0-\infty}$	Area under the concentration time curve from time 0 extrapolated to time infinity
AUC_{0-28d}	Area under the concentration time curve from time 0 to 28 days postdose
AUC_{0-last}	Area under the concentration time curve from time 0 to the timepoint with the last measurable concentration
BCVA	Best-Corrected Visual Acuity
BMI	Body Mass Index
CAS	Clinical Activity Score
CI	Confidence Interval
CL	Clearance
C_{max}	Maximal concentration
C_{min}	Minimal concentration
CS	Clinically Significant
CT	Computed Tomography
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
ETDRS	Early Treatment of Diabetic Retinopathy Study
HR	Heart Rate
IA	Interim Analysis
ICH	International Conference on Harmonisation
IL	Interleukin
IOP	Intraocular Pressure
IV	Intravenous(ly)
λ_z	Terminal elimination rate constant
LOCF	Last Observation Carried Forward
LS	Least Squares

[redacted]

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MRD1	Margin reflex distance 1
MRD2	Margin reflex distance 2
MRI	Magnetic Resonance Imaging
NCA	Noncompartmental Analyses
NCS	Not Clinically Significant
ODO	Observed Data Only
Q4W	Every 4 Weeks
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PDF	Portable Document Format
PI	Principal Investigator
PK	Pharmacokinetics
[redacted]	[redacted]
PT	Preferred Term
QTcF	QT Interval Corrected by Fridericia's Formula
RTF	Rich Text Format
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SRC	Safety Review Committee
$t_{1/2}$	Terminal half-life
TEAE	Treatment-Emergent Adverse Event
TED	Thyroid Eye Disease
T_{last}	Time point with the last measurable concentration
TLF	Tables, Listings and Figures
T_{max}	Time at which the maximal concentration is observed
TSH	Thyroid Stimulating Hormone
TSI	Thyroid Stimulating Immunoglobulin
V_{ss}	Steady-state volume of distribution
V_z	Volume of distribution based on the terminal phase
WHODrug	World Health Organization Drug Dictionary

1. Introduction

This statistical analysis plan (SAP) details the planned analyses and reporting for protocol LASN01-CL-2201, with the United States Version 7.0 dated 15NOV2024, and the European and UK Version 7.1 dated 22NOV2024. The statistical methods herein supersede those in the clinical protocol. Any additional required analyses will be completed and identified in the clinical study report.

This SAP has been prepared with consideration of the latest International Conference on Harmonisation (ICH) E9 Guideline, "Guidance for Industry: Statistical Principles for Clinical Trials," and the latest ICH E3 Guideline, "Guidance for Industry: Structure and Content of Clinical Study Reports."

This study was conducted as proof of concept for evaluation of role of IL-11 in thyroid eye disease (TED). TED trials have assigned a target eye, traditional to trials that deliver drug to one eye. As LASN01 is being administered systemically, there should be no difference between either eye and response in either eye should be considered. Procedurally, the protocol has used the target eye as primary endpoint, however, as the study is signal seeking in nature, the drug is administered systemically (intravenously [IV]), and response in either eye is evaluated in consideration of response. A substantial number of patients did not reconsent to protocol v7.0/7.1, which led to the early termination of the study. Only the primary endpoint (proptosis responder) and total 7-point Clinical Activity Score (CAS; Total CAS) endpoints will be summarized. Other exploratory or secondary endpoints will not be analyzed and the per protocol population has been removed.

2. Study 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	<u>For randomized treatment arms:</u> • Percentage of patients who have received LASN01 (pooled analysis of 300 and 600 mg every four weeks [Q4W]) showing a response in proptosis (≥2 mm decrease from Baseline) in the study eye and separately in either 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 either eye without deterioration (≥2 mm increase) of proptosis in the other 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 either eye without deterioration (≥2 mm increase) of proptosis in the other 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 either eye without deterioration (≥2 mm increase) of proptosis in the other 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 or 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) across both LASN01 treatment arms (pooled analysis of 300 and 600 mg Q4W) and in each individual LASN01 treatment arm (600 mg or 300 mg Q4W) compared with placebo at Weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 65, and 73 
Primary: Safety	
To assess the safety and tolerability of IV administration of LASN01 compared with placebo in patients with TED	For randomized treatment arms: • Treatment-emergent adverse events (TEAEs), 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 For open-label treatment arm(s): • TEAEs, changes in concomitant medications • Changes from Baseline in clinical laboratory evaluations, vital signs, electrocardiograms, ophthalmic assessments, and physical examinations following study drug administration
Secondary: Pharmacokinetics	
To characterize the pharmacokinetic (PK) profile of IV administration of LASN01 in patients with TED	For all treatment arms: • Serum LASN01 concentrations at specified time points
Exploratory: Immunogenicity	
Characterize the immunogenicity of IV administration of LASN01 in patients with TED	For all treatment arms: • Incidences of antidrug antibodies at specified timepoints relative to Baseline
Exploratory: Pharmacodynamics	
To explore the potential pharmacodynamic profile of IV administration of LASN01 in patients with TED	For all treatment arms: • Protein markers in blood relevant to the Interleukin-11 (IL-11) pathway

2.1 Safety Assessments

The safety assessments include the following:

- Adverse Events (AEs)
- Safety Labs (Chemistry, Hematology and Coagulation, Urinalysis, urine drug screen, and additional tests listed in Appendix 2 of the protocol.)
- Best Corrected Visual Acuity (BCVA)
- Visual Field
- Ishihara Color Vision Test
- Slit Lamp Biomicroscopy
- Intraocular Pressure (IOP)
- Dilated Fundoscopy
- Physical Exam
- Body weight and height for body mass index (BMI)
- Vital Signs
- Electrocardiograms (ECG)
- Pregnancy Test

2.2 Statistical Hypotheses

The primary clinical endpoint will be assessed using a one-sided Fisher's exact test at a 0.10 significance level. This analysis combines the 600 mg and 300 mg Q4W treatment arms ("pooled group") and compares them to placebo.

- Null Hypothesis (H_0): At Week 37, the percentage of patients showing a proptosis response in the study eye without deterioration in the fellow eye and separately in either eye is less than or equal in the LASN01 pooled group (300 mg and 600 mg) compared to placebo.
- Alternative Hypothesis (H_1): At Week 37, this percentage is greater in the LASN01 pooled group compared to placebo.

3. Study Design and Procedures

3.1 General Study Design

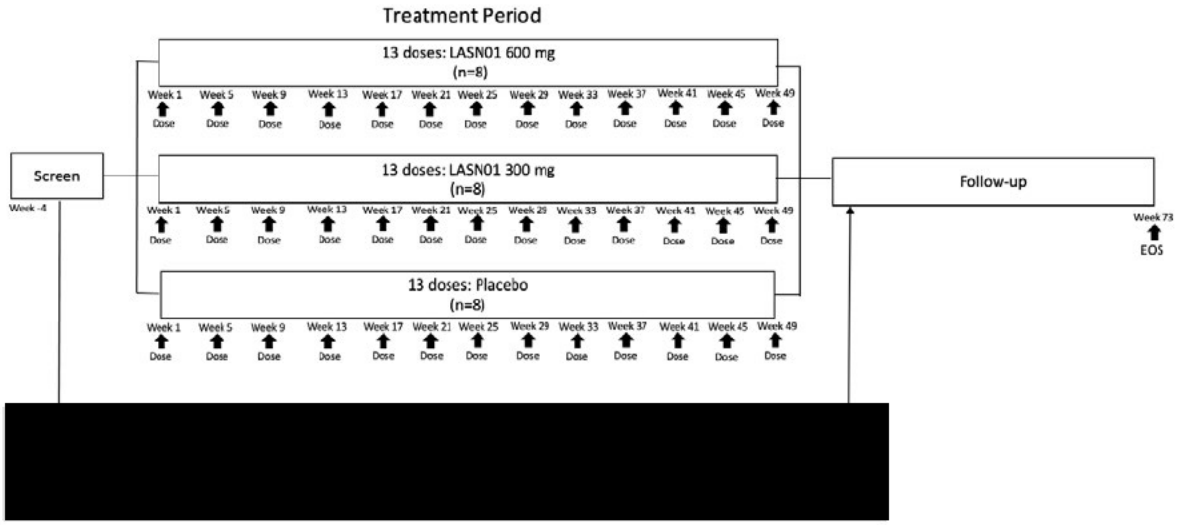
This proof-of-concept Phase 2 study comprises the randomized, double-masked, placebo-controlled treatment arms in patients with TED with no prior anti-IGF-1R treatment [redacted]

The randomized treatment arms will be used to evaluate the efficacy, safety, tolerability, PK, immunogenicity, and PD properties of 2 dose levels (300 and 600 mg) of LASN01 administered IV Q4W 7 to 13 doses in anti-IGF-1R-naïve patients with TED. [redacted]

The general study design for treatment-naïve patients is depicted in Figure 1 for the European protocol version 7.1 and the randomized treatment-naïve patients in the United States protocol version 7.0.

[redacted]

Figure 1. General Study Design for Treatment-Naïve Patients [redacted]



[redacted]

Following 49 weeks of dosing (last dose administered on Day 337), patients will be followed for an additional 24 weeks for a total study duration of 73 weeks (End of Study [EOS] visit on Day 505 ±7 days).

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 [redacted]

A Safety Review Committee (SRC) will be formed to periodically review safety and available PK and PD data. For the randomized, double-masked treatment arms, the SRC will examine masked data. The first data review will occur after at least six patients have been treated and followed for six weeks. Subsequent meetings may take place every 12 months, depending on enrollment rates and SRC discussions. The SRC Charter outlines the committee's structure and provides further conduct details. A separate SRC shell will be created to document and confirm SRC outputs.

Interim analysis (IA) may be performed when at least 50% of evaluable patients in the randomized treatment arms complete at least 8 weeks in the study. [redacted] The IA will include both masked and unmasked outputs for Sponsor review. A separate unmasked statistician

and a separate unmasked programming team will produce unmasked outputs. Designated Lassen Senior Management personnel who are not responsible for study management or decisions that impact data integrity, in accordance with relevant study plans, will review unmasked interim data.

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 (e.g., 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.

Study visits will be referred to in all tables and listings as the scheduled week (e.g., Week 2) corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule.

3.2 Schedule of Assessments and Procedures

See the Schedule of Assessments in Appendix Section 19.1.

3.2.1 Study Treatments

This study will include approximately 36 evaluable patients with TED in 4 treatment arms. Treatment-naïve patients will be randomized (in a 1:1:1 ratio) upon enrollment to LASN01 in either a high-dose (600 mg Q4W ×7-13 doses) or low-dose (300 mg Q4W ×7-13 doses) treatment arm or to placebo. [redacted] Treatment arms for the randomized and open-label patients are shown in Table 1. The protocol was amended as additional safety data became available to increase the duration of treatment with LASN01.

Table 1. 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. Sample Size

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

Randomized Treatment Arms:

- The pooled primary analysis represents a 2:1 randomization of pooled LASN01 (300 mg and 600 mg arms) to placebo with about 24 patients.
- The placebo response rate is assumed to be ~15% (based on Teprotumumab FDA approval data from 2020).
- Assuming a pooled LASN01 response rate of 65% (an absolute treatment effect of 50% over placebo), a sample size of 8 patients per arm provides approximately 81% power at a 10% significance level using a one-sided Fisher's exact test.
- If the placebo response rate is 10%, the power increases to approximately 90% at the same significance level.
- Power calculations were performed using R Version 4.2.1 (R Core Team, 2022), employing simulation methods with 10,000 iterations implemented via the 'statmod' package (Giner, 2016).

[redacted]

[redacted]

5. Analysis Populations

5.1 Efficacy Population

The Efficacy Population includes all randomized patients who received at least 1 dose of study drug and 1 post-dose primary efficacy assessment, with treatment assignment designated according to randomized treatment.

[redacted]

The efficacy population will be used for all efficacy analyses.

5.2 Safety Population

The Safety Population includes all randomized patients who receive at least 1 dose of study drug [redacted] who receive at least 1 dose of study drug. The patients will be analyzed as treated. All safety analyses will be based on the Safety Population.

5.3 Pharmacokinetic Population

The PK Population includes all patients who receive at least 1 complete dose of study drug and for which at least 1 valid PK parameter can be calculated. All PK analyses will be based on the PK Population and will be analyzed as treated.

5.4 Pharmacodynamic Population

The PD Population includes all patients who receive at least 1 complete dose of study drug and who have at least 1 post-therapy PD assessment. All PD analyses will be based on the PD Population and will be analyzed as treated.

6. General Statistical Considerations

6.1 Unit of Analysis

The unit of analysis in this study will be the study eye and either eye for all appropriate ophthalmic summaries. The study eye is determined by the PI or designee as the more severely affected eye at Week 1 (Day 1) before dosing. This will be based on the severity of proptosis in both eyes. If both eyes are

affected equally, the principal investigator (PI) or designee will select the study eye and may take into account other factors such as the CAS. If both proptosis and CAS are equal, the PI or designee will select the study eye and may consider other factors for disease severity per their expert judgement. 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 endpoint. If only one eye is determined to meet the eligibility criteria, that is the study eye by default.

The non-study eye will be referred to as the fellow eye. Fellow eye safety summaries will also be presented as appropriate.

Either eye for responder analyses is defined as the eye that meets responder criteria in either eye (study eye or fellow eye) at Week 37 (Day 253) and the same eye will be analyzed at each visit. If both eyes meet the responder criteria at Week 37 (Day 253) the study eye will be the eye to use in either eye analyses at each visit.

Either eye for continuous Total CAS analyses is defined as the eye that achieves the largest reduction in Total CAS at Week 37 (Day 253), and this single eye will be used for analyses at all visits. If both eyes demonstrate an equal reduction in Total CAS at Week 37 (Day 253), the study eye will be used as the either eye. As a single eye per patient per visit will be analyzed and that eye is held constant for all visits, no additional considerations are needed to account for multiple eyes within a patient.

Non-ocular AEs and medical history will be presented at the patient level.

For ECG and vital sign data that is measured in triplicate, the average of available readings will be the unit of analysis.

6.2 Missing or Inconclusive Data Handling

In general, safety data will not be imputed except for missing or partial dates. The early termination visit will be mapped to the closest scheduled week based on study day. If the patient already has a result in the closest scheduled week, then the early termination visit will be mapped to the next nominal week. Missing efficacy data will be imputed using Last Observation Carried Forward (LOCF) to Week 53 (Day 365). Unscheduled visits will not be carried forward; however, the early termination visit that are mapped to the closest nominal week will be carried forward until Week 53 (Day 365).

Every effort will be made to collect all data at specified times. For the SRC or other IAs, selected AE variables that are missing will be re-coded or imputed as the worst option possible. Missing Relationship to Study Treatment will be re-coded as Related.

6.2.1 Partial or Missing Dates

Partial or missing dates required to identify treatment-emergent or concomitant data will be imputed.

For partial or missing start and end dates of AEs and concomitant medications, the following rules apply:

Partial or Missing Start Dates:

- Missing Day Only: Impute as the 1st of the month, unless the month and year match the first dose date, then impute the day of the first dose.
- Missing Day and Month: Impute as January 1st, unless the year matches the first dose year, then impute the day and month of the first dose.
- Completely Missing Date: Impute as the first dose date unless the end date is on or before the first dose date; in that case, impute as January 1st of the end date's year.

Partial or Missing End Dates:

- Missing Day Only Impute as the last day of the month, unless the month and year match the last dose date, then impute the day of the last dose.
- Missing Day and Month: Impute as December 31st, unless the year matches the last dose year, then impute the day and month of the last dose.
- Ongoing Flag Missing or "Yes": Do not impute the end date unless a death date is available; then impute as the death date.
- Ongoing Flag "No": Impute the missing end date as the last dose date.
- Lost to Follow-Up or Withdrawal Without End Date: Use the last known participation date as the end date.
- Imputed Date After Death Date: Set the end date equal to the death date.

Original dates will be displayed in data listings, and imputed dates will be used only for derivations (e.g., study day, treatment-emergent status.

6.2.2 Definition of Baseline

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.

6.3 Data Analysis Conventions

Ora will perform all data analyses described in this SAP using [redacted]. Outputs will be provided in RTF for tables and figures, and in PDF for tables, listings, and figures (TLFs) in landscape orientation. Each formal TLF deliverable will include three combined PDF files, one for each of the output types.

Data will be summarized and listed separately. Continuous variables will be summarized using the number of patients (n), mean, standard deviation (SD), median, minimum, and maximum. Additionally, coefficient of variation (CV%), geometric mean and geometric CV% will be provided for PK concentrations and parameters (except for T_{max}). Values of 0 will be considered missing when calculating the geometric means. Categorical data will present counts and percentages within each category. Standard Error (SE) may be added to continuous efficacy outputs for Total CAS. Individual patient data listings will also be produced. For all other parameters except for PK concentrations and PK parameters, minima and maxima will retain the same precision as raw values; means and medians will have one additional decimal place; SDs will have two additional decimal places. For PK concentrations and parameters except n, all other descriptive statistics will be presented with the same number of significant digits as raw PK concentrations (3 significant figures). Percentages will be rounded to one decimal place (e.g., XX.X%). Differences between active treatment and placebo will be calculated as Active – Placebo, and change from baseline as Follow-up Visit – Baseline.

Unless otherwise specified, all statistical tests will be one-sided at a significance level of α=0.1. Confidence intervals (CIs) for differences between treatment arms will be two-sided at 95% confidence unless stated otherwise. All p-values will be rounded to four decimal places; p-values less than 0.001 will be shown as "<0.001," and those greater than 0.9999 as ">0.999."

Summaries will be presented by treatment arm, including 300 mg, 600 mg, pooled treatment group (300 mg and 600 mg) for efficacy, placebo arm, [redacted] and, where appropriate, by visit and eye (study eye and either eye). Where possible, p-values will be displayed for comparisons of relevant active treatment groups to placebo; [redacted]. Listings will be presented by patient number, treatment arm, visit, time point, and parameter as applicable based on enrolled patients unless otherwise specified.

Masked SRC and masked IA outputs will generally reference the following 3 treatment groups unless otherwise specified in the shells:

- Treatment-Naïve group (pooled LASN01 300 mg, LASN01 600 mg, placebo)
- [redacted]
- All Patients

Unmasked IAs, topline, and final analysis outputs will generally reference 4 arms (LASN01 300 mg, LASN01 600 mg, placebo, [redacted]) for dispositional and safety outputs unless otherwise specified in the shells.

The All Patients group (including patients from LASN01 300 mg, 600 mg, placebo, and [redacted]) will be presented for the IA and may be presented for the final output where indicated in the shells.

Safety tables for the final analysis will include the LASN01 300 mg, LASN01 600 mg, [redacted], placebo, and All Patients columns.

6.4 Adjustments for Multiplicity

As this is an early-phase proof-of-concept study, there is no strong control of the family-wise error rate (alpha = 0.1), and there are no multiplicity adjustments for the primary or secondary efficacy endpoints.

7. Disposition of Patients

Patient disposition will be presented in terms of the number of patients who were randomized to masked study medication [redacted], with subcategories of treated patients. The number and percentages of patients will be summarized for the analysis populations including the Efficacy, Safety, PK, and PD Populations. Number and percentage of patients who completed the study and discontinued from the study will be summarized. Patients who are not discontinued from the study will be considered study completers. Number and percentage of patients who completed treatment and discontinued the treatments early will be summarized. Completing treatment will be based on the patients' most recent consented protocol version. Disposition will be summarized by treatment arm, including LASN01 300 mg, LASN01 600 mg, placebo, [redacted], and overall for all patients. Percentages will be calculated using randomized (or enrolled patients) as the denominator unless otherwise specified.

The reasons for premature study discontinuation and treatment discontinuation will be summarized by treatment arm and overall for all discontinued patients. Percentages will be calculated using discontinued patients as the denominator. The reasons for study discontinuation that will be summarized include: Death, Lost to Follow-up, Physician Decision, Protocol non-compliance with protocol procedures, Study Termination, Withdrawal of Consent, and Other. The reasons for treatment discontinuation that will be

summarized include: Adverse Event, Non-compliance with study drug administration or other protocol procedures, Physician Decision, Pregnancy, Prohibited Concomitant Medication, Study Termination, Withdrawal of Consent, and Other. A patient listing will be provided that includes the date of and reason for premature study and treatment discontinuation.

The number and percentage of patients with any, major, or minor deviations, based on the "Severity" category collected from the Clinical Trial Management System (CTMS), will be summarized by treatment arm and overall for all patients. A patient listing will be provided that includes the date of the deviation, the deviation category, the deviation description, and CTMS variables (Reported to IRB and Severity). Severity of whether the deviation was judged to be important/major or minor will be determined by the clinical team and the sponsor before the database lock.

Listings will be provided that include informed consent date, protocol version, country of participation, meeting eligibility criteria or not, date of TED symptom onset, study eye, and exclusions from analysis populations with reasons for exclusions. Randomization, including previous teprotumumab, randomization date, randomization number, randomized treatment, and actual treatment, will be included within patient listings.

8. Demographic and Baseline Disease Characteristics

8.1 Demographic and Baseline Characteristic Variables

Demographics and baseline characteristics will be summarized by treatment arm and overall for all patients using continuous or categorical descriptive statistics based on the Safety Population.

The following demographic variables will be presented: age, age category, sex, ethnicity, race , and iris color for study eye and fellow eye.

The following baseline characteristics will be presented: baseline proptosis from Hertel for study eye and fellow eye, baseline Total CAS for study eye and fellow eye, height, weight, BMI, smoking history, duration of TED in months (Week 1 [Day 1] Date – Onset of TED symptoms), duration of Graves' Disease in years (Week 1 [Day 1] Date – Graves diagnosis date), history of teprotumumab response, country of participation, free triiodothyronine, free thyroxine, thyroid stimulating immunoglobulin (TSI), and thyroid stimulating hormone (TSH).

Patient listings that include all demographic variables (year of birth, age, sex, childbearing potential, race, ethnicity, and iris color) will be provided. Baseline characteristics can be found on their respective listings.

9. Medical History, Medications, and Procedures

Medical history and medication listings will be generated separately for ocular and non-ocular data. Prior and concomitant procedures will be listed.

The medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version as specified in the Data Management Plan (DMP). Listings of ocular and non-ocular medical history will be provided.

9.1 Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug), with the version specified in the DMP.

Prior medications are those with an end date before the initiation of the study drug. Concomitant medications are those taken (1) before initiation of study drug administration and continuing after the first administration, or (2) at any time following the first administration of the study drug.

Both prior and concomitant medications will be listed. Ocular and non-ocular outputs will be generated separately.

A separate listing will be presented for current TED treatments.

9.2 Prior and Concomitant Procedures

Prior and concomitant procedures will be coded using MedDRA with the version specified in the DMP. Prior and concomitant have the same definitions as the medications stated in Section 9.1 but for procedures. A listing of prior and concomitant procedures will be provided.

[redacted]

10. Dosing Compliance and Treatment Exposure

In addition to the analyses described in the following sections, patient listings will be provided for study drug administration.

10.1 Dosing Compliance

The number of actual doses received will be calculated from the number of infusions recorded in the study drug administration electronic Case Report Form (eCRF). The number of expected doses will depend on which protocol amendment the patient is consented to, regardless of study completion status.

Number of doses received will appear on the Disposition listing; otherwise, study drug administration will have its own listing.

10.2 Treatment Exposure

Extent of treatment exposure for completed or discontinued patients will be calculated in days using the following:

Extent of Exposure (days) = (Date of Last Dose - Date of First Dose) + 1

Extent of treatment exposure for each patient exposed to study drug will be summarized with continuous descriptive statistics for each treatment arm, pooled active group (300 mg and 600 mg), and for all patients using the Safety Population.

11. Efficacy Analyses

11.1 Analysis of Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the percent of patients showing a response in proptosis measured using Hertel exophthalmometer (≥2 mm decrease from baseline) in the study eye and separately in either eye without increased proptosis (≥2 mm increase) in the other eye at Week 37 (Day 253) as measured by Hertel Exophthalmometer. The primary efficacy endpoint will be assessed with a one-sided Fisher's exact p-value comparing the pooled active group to placebo at each visit, including the primary endpoint visit at Week 37. Interpretation of statistical significance should be made at the α=0.1 level. Two-sided 95% CIs for responder analyses may be calculated with the Clopper-Pearson exact method.

Fisher's exact test syntax:

```
Proc sort data = <data>;
      by TRTPN descending AVALC; *orders the responses;
run;

proc freq data=<data> order=data; *Keeps the order in the dataset;
      tables TRTPN*AVALC / fisher;
run;
```

where `TRTPN` is planned treatment (1=Active and 2=Placebo)

AVALC is the responder variable (Y = response in proptosis of ≥2 mm decrease from baseline in the study eye and separately in either eye and <2 mm increase in the other eye; and N = response of < 2 mm decrease from baseline in the study eye and separately in either eye or ≥2 mm increase in the other eye).

Note: with the above ordering, the right-sided p-value will be the correct one-sided p-value from Fisher's exact test for the primary hypothesis.

The primary efficacy analysis will utilize the Efficacy Population with LOCF. Additional sensitivity analysis may be conducted on the primary efficacy endpoint with observed data only (ODO) using study eye.

The percentage of proptosis responders by treatment arm (pooled active group and placebo) over time through Week 37 using line graphs for the Efficacy Population with LOCF will be produced for study eye and either eye separately.

Tables and figures will be provided for the individual treatment groups and pooled active group for all available visits while Week 37 remains the primary endpoint. [redacted]. A listing of proptosis in both eyes will be provided.

11.2 Analysis of the Secondary Efficacy Endpoints

The Efficacy Population with LOCF will be used for secondary endpoint analyses. All secondary endpoints will be presented in patient listings by visit and eye where appropriate, however, summary tables will be created for CAS only.

11.2.1 Clinical Activity Score

The CAS measures the presence (scored as 1) or absence (scored as 0) of the following signs and symptoms:

- Spontaneous orbital pain
- Gaze-evoked orbital pain
- Eyelid swelling due to active TED
- Eyelid erythema
- Conjunctival redness due to active TED
- Chemosis
- Inflammation of the caruncle or plica

Total CAS is the sum of these scores and is measured at the appropriate visits according to the schedule of assessments. A CAS responder is defined as patients achieving a Total CAS score of 0 or 1 at a post-baseline visit. A CAS Responder must have at least a score of 2 at baseline to be included in analyses. Study eye and either eye responder analyses will use a one-sided Fisher's exact p-value to compare the individual treatment arms and pooled active group to placebo at each visit. [redacted] Two-sided 95% CIs for responder analyses may be calculated with the Clopper-Pearson exact method.

Total CAS and its change from baseline results will be summarized for each visit with descriptive statistics for each individual arm and the pooled active group. P-values for the one-sample t-tests will be provided to assess each individual arm and the pooled treatment arm change from baseline. The 95% CIs may also be constructed around the treatment difference, and p-values from a two-sample t-test will be provided to assess the individual treatment arm and the pooled active treatment differences as compared to placebo. An analysis of covariance (ANCOVA) model with baseline and treatment group as fixed factors will be used to compare pooled active group to placebo for study eyes and separately for either eyes at each visit.

A restricted maximum likelihood-based mixed model repeated measures (MMRM) analysis of the longitudinal observations at each post-baseline visit will be used to model change from baseline in Total CAS in the study eye only. The model will include the categorical effects of treatment (pooled 300 mg and 600 mg, and placebo), visit (visits through Week 37), and the continuous covariate of baseline proptosis as fixed factors, and within-patient errors will be modeled using the repeated statement. An unstructured-covariance matrix will be used to model the within-patient error. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in this order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, and autoregressive. The Kenward-Roger method will be used to determine denominator degrees of freedom. The overall least squares (LS) means and corresponding SEs, 95% CIs, and p-values (only for treatment comparisons) for pooled active group, and for the treatment difference compared to placebo may be presented though Week 37.

MMRM syntax:

```
proc mixed data=<data>;
    class AVISITN TRTPG1 SUBJID;
    model CHG = BASE AVISITN TRTPG1 /ddfm=KR;
    repeated / subject=SUBJID type=UN;
```

```
    lsmeans TRTPG1 / cl pdiff;
    ods output lsmeans=LS diffs=DIFFS;
run;
```

where

- AVISITN is the visit as a categorical variable with visits up to and including Week 37
- TRTPG1 is the treatment groups, pooled active group, and placebo
- CHG is the change from baseline for all patients
- BASE is the baseline score for all patients
- LS and DIFFS are the respective output datasets

Actual and mean change from baseline in Total CAS will utilize the Efficacy Population with LOCF in study eye and either eye. Responder analyses will utilize Efficacy Population with LOCF in study eye and either eye; and Efficacy Population with ODO in study only. The MMRM analysis will utilize Efficacy Population with ODO in study eye only.

Figures for Total CAS responders over time in the study eye and separately in either eye as well as change from baseline over time in the study eye and separately in either eye for the Efficacy Population with LOCF will be presented. The CAS assessment will also be presented in a listing.

11.2.2 Clinical Assessment of Spontaneous Orbital Pain, Gaze Evoked Pain, Conjunctival Redness, Chemosis, and Eyelid Swelling

Spontaneous orbital pain assessment, gaze evoked pain assessment, conjunctival redness grade, chemosis grade, and eyelid swelling grade will be collected. These are being assessed independently from CAS as exploratory clinical severity endpoints. The assessments will be presented in listings.

11.2.3 Upper and Lower Eyelid Retraction based on MRD1 and MRD2

Eyelid retraction is defined as a displacement of the upper eyelid superiorly or lower eyelid inferiorly. Measurements consist of the MRD1 (margin reflex distance 1; upper lid) and MRD2 (margin reflex distnace 2; lower lid) in mm. Measurements are assessed at all visits according to the schedule of assessments. The assessments will be presented in listings.

11.2.4 LID APERTURE

Lid aperture is defined as the distance between the lid margins in millimeters with the patient looking in the primary position, sitting relaxed and with distant fixation. Lid aperture will be based on lid aperture measurements, which will be presented in listings.

11.2.5 DIPLOPIA USING THE BAHN-GORMAN SCALE

Diplopia, or double-vision, will be assessed with the Bahn-Gorman Scale with the following responses:

- Grade 0 – No diplopia present
- 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

Diplopia is assessed at all appropriate visits according to the schedule of assessments. The assessments will be presented in listings.

11.2.6 LAGOPHTHALMOS AND VON GRAEFE'S SIGN

Presence or absence of lagophthalmos and Von Graefe's Sign are assessed at the appropriate visits according to the schedule of assessments. The assessments will be presented in listings.

11.2.7 EXTRAOCULAR MOVEMENTS

Extraocular movements in all 4 primary directions (up, down, nasal, and temporal) will be performed at all appropriate visits according to the schedule of assessments and will be recorded in degrees using the Hirschberg method. Adduction (inward or medial movement toward the nose), abduction (outward or lateral movement toward the ear), supraduction (upward vertical rotation around the horizonal axis), and infraduction (downward vertical rotation around the horizonal axis) will be recorded. The assessments will be presented in listings.

11.3 Analysis of the Exploratory Efficacy Variables

11.3.1 ORBITAL IMAGING AND FACIAL PHOTOGRAPHY FROM CENTRAL READING CENTER

Axial high-resolution images will be obtained locally and transmitted to a central radiology vendor for review. Besides assessment of proptosis, the orbital magnetic resonance imaging (MRI) sequences may provide (but are not limited to) volumetric analysis (in mm^3) of orbital compartments such as individual extraocular

muscle volume and total muscle volume, orbital fat volume, fibrosis measurement of each muscle and average fibrosis of all 4 four muscles per eye. These will be measured at screening and for all visits according to the schedule of assessments and will all be presented as listings. The proptosis listing will include both proptosis readings and the average reading for each visit for the study and fellow eye.

A facial photography assessment will also be done per the ophthalmology manual. Facial photography measurements may be performed and, if present, these will be presented as a listing.

In the US only, an orbital computed tomography (CT) scan may be performed if the patient cannot have an MRI scan.

12. Safety Analyses

All safety analyses will be conducted using the Safety Population. Safety endpoints will be summarized for the LASN01 300 mg, LASN01 600 mg, [redacted], placebo, and for the All Patients treatment arms.

12.1 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens by clinically meaningful amount on or after the first dose of study drug administration. Only TEAEs will be summarized, however all AEs collected in the eCRF will be presented in data listings. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version as specified in the DMP.

An overall summary will be presented that includes the number of events and the number and percentage of patients who experienced at least one TEAE by treatment arm and overall for all patients. This summary will also include breakdowns of TEAEs further categorized as ocular or non-ocular, serious TEAEs, related TEAEs, TEAEs leading to early treatment discontinuation, TEAEs leading to early study discontinuation, TEAEs leading to death, and Serious TEAEs by maximal severity.

Additional summaries of TEAEs classified by MedDRA SOC and PT will be provided showing the number of events and the number and percentage of patients who experienced at least one TEAE by treatment arm and overall for all patients. If a patient reports multiple TEAEs to the same SOC or multiple PTs within the same SOC, the patient will be counted only once within that SOC or PT. In the summaries, SOCs and PTs within the SOC will be listed in descending frequency order for the All Patients column.

Separate summaries by SOC and PT will be provided for the following categories of AEs:

- TEAEs

- Related TEAEs
- TEAEs by maximal severity grade
- Serious TEAEs by maximal severity grade
- Related TEAEs by maximal severity grade

The number of patients with any TEAEs (along with percentages) will be tabulated by SOC and PT within each SOC by treatment arm and overall for all patients. To count the number of patients with any TEAEs, if a patient has multiple TEAEs coded to the same SOC or PT within an SOC, the patient will be counted once under the maximum severity.

All TEAEs will be presented in a patient listing. In addition, serious TEAEs, related TEAEs, and TEAEs leading to death will be listed separately.

12.2 Best Corrected Visual Acuity

Best corrected visual acuity (BCVA) letter score will be measured at 4 meters using an Early Treatment Diabetic Retinography Study (ETDRS) chart. If the patient reads letters at 4 meters, the BCVA letter score will be 30 letters plus the 4 meter result. If the patient reads less than 20 letters at 4 meters, the letter score will be the sum of the 1-meter and 4-meter results. If the patient is unable to read letters at 1 and 4 meters then count fingers, hand motion, and light perception will be assessed. The Snellen equivalent to the letter score will also be collected. BCVA is measured at each visit.

For BCVA letter score, the observed and change from baseline will be summarized for each eye (study eye and fellow eye) using continuous descriptive statistics by visit for each treatment arm and for all patients. Counts and percentages of patients with a 15-letter loss will also be summarized for the change from baseline. A patient listing of BCVA will also be produced.

12.3 Visual Field

Visual field will be assessed using either a 10-2, 24-2, or 30-2 assessment as per the schedule of assessments. The results will be graded as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS).

The visual field results data will be summarized by grade of normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS) for each treatment arm and for all patients at each visit for each eye (study eye and fellow eye). Percentages will be based on the number of patients in each treatment arm with normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS) responses. A patient listing of the visual field results will also be produced.

12.4 Ishihara Color Vision Test

Color vision will be assessed with the Ishihara Test which uses a series of multi-colored plates. Color vision will be assessed as per the schedule of assessments. The number of plates correct, and the total number of plates shown will be collected. A patient listing of the Ishihara Color Vision results will be produced.

12.5 Slit Lamp Biomicroscopy

A slit lamp biomicroscopy examination of the cornea, conjunctiva, anterior chamber, iris, lens, eyelid, and pupil will be performed as per the schedule of assessments. The results will be graded as normal, abnormal NCS, or abnormal CS.

The results will be summarized using numbers and percentages for each treatment arm and for all patients at each visit for each eye (study eye and fellow eye). Percentages will be based on the number of patients in each treatment arm with responses and overall for all patients. Summary table will be presented for normal, abnormal NCS, or abnormal CS in cornea, conjunctiva, anterior chamber, iris, lens, eyelid, and pupil. A patient listing of the slit lamp biomicroscopy parameters will also be produced.

12.6 Intraocular Pressure

Patients' IOP will be assessed in each eye per the schedule of assessments. Results will be taken from a single measurement and will be recorded in millimeters of Mercury (mmHg). For IOP, the mean values and mean change from baseline will be summarized for each eye (study eye and fellow eye) using continuous descriptive statistics by visit for each treatment arm and for all patients. A patient listing of IOP will be produced.

12.7 Dilated Fundoscopy

A dilated fundoscopy examination of the vitreous, retina, macula, optic nerve, and choroid will be performed as per the schedule of assessments. The results will be graded as normal, abnormal NCS, or abnormal CS.

The results will be summarized using numbers and percentages for each treatment arm and for all patients for each eye (study eye and fellow eye). Percentages will be based on the number of patients in each treatment arm with responses. Summary table will be presented for normal, abnormal NCS, or abnormal CS in the vitreous, retina, macula, optic nerve, and choroid. A patient listing of the dilated fundoscopy parameters will also be produced.

12.8 Physical Examination

Per the eCRF completion guidelines, a complete or brief physical examination will take place per the schedule of assessments. Complete and brief physical exam results for each body system will be graded as normal, abnormal NCS, or abnormal CS. Complete and brief physical exam results will be summarized by treatment arm and for all patients using numbers and percentages at each visit. A patient listing of the physical examination results will also be produced.

12.9 Height, Weight, and BMI

Height (cm), Weight (kg), and body mass index (BMI [kg/m^2]) will be summarized with continuous descriptive statistics for each visit and treatment arm and for all patients. Height will be measured at baseline only. BMI will be calculated at Screening and Baseline. Weight will be measured per the schedule of assessments. Baseline height, weight, and BMI will be summarized on the demographics and baseline characteristics table. Change from baseline for Weight (kg) will be summarized by treatment arm and for all patients. A patient listing of the height, weight, and BMI results will also be produced.

12.10 Vital Signs

Vital signs, including seated pulse rate, systolic and diastolic blood pressure, body temperature, and respiration rate will be summarized with continuous descriptive statistics at each planned data collection visit and time point by treatment arm and for all patients. On dosing days, vital signs will be assessed pre-dose and at 1 and 2 hours (±15 minutes each) following the start of infusion. Mean vital signs and mean change from baseline will also be summarized to each post-baseline visit and time point. A patient listing of the vital signs results will also be produced.

12.11 Electrocardiogram

Electrocardiograms (ECGs) will be measured in triplicate within a 15-minute period, separated by 1 minute or more. Heart rate (HR), and the PR, RR, QRS, QT, and QTcF (QT interval corrected using Fridericia's formula) intervals will be summarized using continuous descriptive statistics by treatment arm and for all patients at each planned data collection visit and time point. Change from baseline to each post-baseline visit and time point will be also summarized by treatment arm.

A patient listing of the ECG results will be produced. The results for ECG will also be graded as normal, abnormal NCS, or abnormal CS, and these ECG results will be listed only.

12.12 Clinical Laboratory Data

Clinical laboratory data including hematology, coagulation, serum chemistry, urinalysis, urine drug screen, and additional tests (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 polymerase chain reaction (PCR) antibody test, serum or urine pregnancy [for females of childbearing potential only]) are collected at each planned data collection visits.

The quantitative variables will be summarized by treatment arm with continuous descriptive statistics. Change from baseline will also be summarized by treatment arm and for all patients. Categorical results will not be summarized. Listings will be produced including an additional listing for abnormal values only.

13. Pharmacokinetic Analyses

PK will be assessed using the PK Population. placebo patients will not be assessed for PK. Where the data allow, noncompartmental analyses (NCA) will be used to estimate Day 1 serum PK parameters for LASN01 after single and repeat IV dosing. Final analyses will be performed after the database lock and will use actual sampling times. The effect of antidrug antibodies (ADA) on LASN01 exposure will be assessed. A PK report will be generated summarizing the results.

[redacted]

13.1 Summary of Concentration Versus Time Data

LASN01 concentration data will be summarized by study treatment arm (LASN01 300 mg, LASN01 600 mg, [redacted]) and nominal time using descriptive statistics. Linear and semi-logarithmic plots of the individual patient Day 1 LASN01 serum concentrations versus actual time data will be generated. Additionally, a comparison of the treatment arms (low versus high dose) will be shown graphically using linear and semi-logarithmic plots of the arithmetic mean (with SD) serum concentrations versus nominal time data. A patient listing of all serum LASN01 concentrations will be provided.

Individual and arithmetic mean (with SD) LASN01 concentrations from the predose samples obtained throughout the study will be plotted versus Study Day.

13.2 LASN01 Pharmacokinetics

Where the data allow, LASN01 serum concentration versus time data will be subjected to NCA. Individual patient serum concentration versus time data will be downloaded into validated [redacted] for PK analyses. Actual sample collection times relative to the time of dosing will be used for the final PK calculations (actual sampling time for predose samples will be set to zero).

Where appropriate, the following LASN01 serum parameters will be generated:

C_{max}	Maximal concentration
C_{min}	Minimal concentration (i.e., predose trough concentration; For Day 1, this value will be obtained from the Day 29 predose sample)
T_{max}	Time at which the maximal concentration is observed
T_{last}	Time point with the last measurable concentration
$AUC_{0\text{-}28d}$	Area under the concentration time curve from time 0 to 28 days post-dose; calculated using the linear up/log down trapezoidal rule
$AUC_{0\text{-}inf}$	Area under the concentration time curve from time 0 extrapolated to time infinity; calculated as $AUC_{0\text{-}last} + (C_{last}/ \lambda_z)$ where C_{last} is the predicted concentration at T_{last}
$AUC_{0\text{-}last}$	Area under the concentration time curve from time 0 to the time point with the last measurable concentration; calculated using the linear up/log down trapezoidal rule
λ_z	Terminal elimination rate constant; estimated by linear regression of the log concentration versus time curve
$t_{1/2}$	Terminal half-life; calculated as $\ln(2)/\lambda_z$, where λ_z is the terminal elimination rate constant
CL	Clearance; calculated as dose/$AUC_{0\text{-}inf}$
V_{ss}	Steady-state volume of distribution; calculated as $MRT_{0\text{-}inf}$/CL where $MRT_{0\text{-}inf}$ is the mean residence time extrapolated to time infinity

V_z Volume of distribution based on the terminal phase; calculated as dose/(λ_z x $AUC_{0\text{-}inf}$)

Three measurable time points must be available in the concentration versus time profile for AUC values to be reported. Parameters based on the terminal phase of the concentration versus time data will only be reported if the following acceptance criteria are met: there are a minimum of 3 time points with measurable LASN01 concentrations in the terminal phase of the PK profile (not including C_{max}), $R^2 > 0.9$, and the percent of $AUC_{0\text{-}\infty}$ extrapolated from the last measurable concentration to time infinity ($AUC_{\%extrap}$) < 20%. Uniform data weights will be selected as part of the regression step options.

Predose values trough (C_{min}) and end of infusion values over the course of the study will be evaluated for accumulation compared to the trough value after the Day 1 dose.

A patient listing of PK parameters will be provided. Individual concentration values for PK parameters may be excluded from the calculation of descriptive statistics and graphical displays, e.g., due to a deviation of actual versus planned sampling time, dosing error, dosing holiday, or obvious outlier. Any excluded data, however, will be listed along with the reason for exclusion.

13.3 Statistical Assessment of Dose-Proportionality

Dose proportionality of study drug will be assessed for parameters C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}28d}$, and $AUC_{0\text{-}inf}$, using the power model:

$$\ln(\text{Parameter}) = \beta_0 + \beta_1 \times \ln(\text{Dose})$$

Dose proportionality will be evaluated by estimating the slope (β_1) along with its 90% CI. The power model will be fit by restricted maximum likelihood (REML) using [redacted] with both the intercept and slope terms as fixed effects. The predefined dose proportionality criterion over the dose range will be met if the 90% CI for β_1 is within 0.8 to 1.25. Dose proportionality will only be checked between the LASN01 600 mg and LASN01 300 mg treatment arms.

14. Pharmacodynamic Analyses

The Pharmacodynamic Population will be used to summarize counts and percentages of patients with positive and negative responses of ADA for LASN01 300 mg, LASN01 600 mg, [redacted] at each visit. Percentages will be based on the number of patients in each treatment arm with responses at the visit. A table and a listing will be presented.

15. Interim Analyses

An interim analysis was completed when approximately 50% of evaluable patients enrolled in the randomized treatment arms completed at least 8 weeks in the study. The interim analysis contained both masked and unmasked outputs for the Sponsor's review. Unmasked outputs were prepared by designated unmasked personnel not otherwise involved in study conduct to avoid operational bias. As this is an early phase proof-of-concept study where control over the type-1 error rate is not required, the alpha remained at 0.1.

Masked IA outputs included a Treatment-Naïve Active group (consisting of all the randomized treatment naive patients), [redacted], and an All Patients arm. Since masked table summaries had a different column structure, masked tables were added to the IA for patient dispositions, demographic and baseline characteristics, and TEAEs by SOC and PT. Efficacy output for the IA had the same column structure for both Masked and Unmasked outputs.

16. Changes from Protocol-Stated Analyses

The following changes from protocol-stated analyses are made to the SAP by the sponsor:

Due to several consent withdrawals and patients declining to reconsent for the 12-month extension, the Sponsor unmasked the clinical team to assess whether early study termination was appropriate. Investigators, the CRO clinical operations team, and CRO statisticians remained masked until the database lock. The following specific changes have been made and the additions are considered exploratory:

- Due to early termination of the study, only proptosis measured by Hertel and Total CAS will be analyzed in tables. Other secondary and exploratory endpoints will be listed.
- Either eye responder analyses have been added for proptosis by Hertel and Total CAS, and either eye continuous analyses have been added for Total CAS. Either eye responder and continuous Total CAS analyses will identify an eye at Week 37 (Day 253) and use that same eye in the analysis for each visit.
- A sensitivity analysis, as defined in protocol Section 9.2.4, has been added for Total CAS in the study eye and separately for either eye. Only the pooled active group will be compared to placebo. The sensitivity analysis of the primary responder rate for proptosis from protocol Section 9.4.2. has been removed.

- An ANCOVA model has been added to existing mean and mean change from baseline Total CAS tables. The model includes baseline and treatment as factors and will be run separately for each eye (study eye and either eye) and visit. Only the pooled active group will be compared to placebo.
- 95% CI for proptosis responder analysis has been removed
- LOCF has been added as the imputation method for missing data for all efficacy analyses.
- Per Protocol Population analyses have been removed.
- ODO analyses have been added for all proptosis and CAS tables to check robustness of results.

17. References

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[redacted]