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Protocol Number: SUN-131-03

Study Title:

A Multi-Center, Double-Masked, Randomized, Placebo-Controlled Evaluation of the Safety and Efficacy of SUN 131 Transdermal System (TDS) as Compared to Placebo TDS in Patients with a Chalazion

Protocol Version & Date: Version 2.0: 30 Aug 2018

CLINICAL STUDY PROTOCOL

Study Title:	**A Multi-Center, Double-Masked, Randomized, Placebo-Controlled Evaluation of the Safety and Efficacy of SUN-131 Transdermal System (TDS) as Compared to Placebo TDS in Patients with a Chalazion**
Protocol Number:	**SUN-131-03**
Study Drug:	**SUN-131 1.5% TDS**
US IND Number:	**115225**
Indication:	**Treatment of a Chalazion**
Sponsor:	**Senju USA, Inc.**
Development Phase:	**Phase 3**
Sponsor's Responsible Medical Monitor:	[redacted]
Contact Information:	**Senju USA, Inc.** 21700 Oxnard Street, Suite 1070 Woodland Hills, CA 91367 Phone: (818) 719-7190
Protocol Version & Date:	**Version 2.0: 30 Aug 2018**

PROTOCOL APPROVAL PAGE

Document Number: **SUN-131-03 Protocol (SUN-131-03)**

Document Title: **A Multi-Center, Double-Masked, Randomized, Placebo-Controlled Evaluation of the Safety and Efficacy of SUN-131 Transdermal System (TDS) as Compared to Placebo TDS in Patients with a Chalazion**

Protocol Version: **Version 2.0**

Protocol Date: **30 AUG 2018**

This protocol has been fully reviewed by the study sponsor, Senju USA, Inc., and has been approved by the sponsor. The following persons contributed to the writing and/or approval of this protocol:

Signature: _____ **Date:** _____

Signature: _____ **Date:** _____

Takahiro Ogawa, PhD
President
Senju USA, Inc.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	Activities of Daily Living
AE	Adverse Event
CFR	Code of Federal Regulation
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eDCF	Electronic Data Clarification Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IWRS	Interactive Web-Based Response System
LC/MS-MS	Liquid Chromatography-Mass Spectrometry
LLOQ	Lower Limit of Quantification
MAD	Multiple Ascending Dose
MKP-1	Mitogen-Activated Protein Kinase Phosphatase-1
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NCI	National Cancer Institute
PI	Principal Investigator

Abbreviation	Definition
PP	Per-Protocol
PRO	Patient Reported Outcome
REB	Research Ethics Board
SAD	Single Application Dose
SAE	Serious Adverse Event
SoC	Standard of Care
SOC	System Organ Class
TDS	Transdermal System
TEAE	Treatment Emergent Adverse Event
US	United States
VA	Visual Acuity
VAS	Visual Analog Scale
WHO	World Health Organization

INVESTIGATOR STATEMENT

I have read and understand the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the sponsor's guidelines, all applicable government regulations, and the International Council for Harmonisation Good Clinical Practice Guidelines E6 (ICH GCP).

I will maintain accurate source documents from which data are entered onto electronic case report forms and accurate drug accountability records that show the receipt and disposition of all study drugs.

I will provide adequate protocol training to my associates, colleagues, and employees assisting in the conduct of the study.

I will obtain Institutional Review Board/Ethics Committee (IRB/EC) approval of the protocol and Informed Consent Form (ICF) prior to enrollment of subjects in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the IRB/EC prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will ensure that a fully executed IRB approved ICF is obtained from each subject prior to initiation of any study procedures.

I will report (within 24 hours) any serious adverse event (SAE), regardless of relationship to study drug, or pregnancy that occurs during the course of the study, in accordance with the procedures described in Section 6 of the protocol. I will notify the sponsor if I become aware that a partner of a study subject becomes pregnant while the subject was receiving this study drug.

I will submit all protocol inclusion/exclusion violations to the medical monitor for approval prior to enrollment of the subject in the study.

I will allow the sponsor, Senju USA, Inc. and its agents, as well as the United States (US) Food and Drug Administration (FDA) and other regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring subject confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify the sponsor as soon as possible thereafter (no later than 1 week).

This protocol contains information that is proprietary to Senju USA, Inc. The information contained herein is provided for the purpose of conducting a clinical trial for Senju USA, Inc.

The contents of this protocol may be disclosed to study personnel under your supervision and to your IRB/EC. The contents of this protocol may not be disclosed to any other parties (unless such disclosure is required by government regulations or laws) without the prior written approval of Senju USA, Inc.

_____ _____

Investigator's Signature Date

SYNOPSIS

Study Title (Protocol Number)	A Multi-Center, Double-Masked, Randomized, Placebo-Controlled Evaluation of the Safety and Efficacy of SUN-131 Transdermal System (TDS) as Compared to Placebo TDS in Patients with a Chalazion (SUN-131-03)
Phase	Phase 3
Study Drug	SUN-131 1.5% TDS
Objectives	To evaluate the efficacy and safety of SUN-131 1.5% TDS as compared with placebo TDS in the treatment of chalazion
Study Design	This is a prospective multi-center, double-masked, randomized, placebo-controlled clinical trial. Subjects will be centrally randomly assigned in a 1:1 ratio to receive one of the following treatments in the affected eyelid: SUN-131 1.5% TDS (n = 130) Placebo TDS (n = 130) The randomization will be stratified by age group (<12 years, ≥12 years). All study drug will be worn for a minimum of 16 hours and a maximum of 24 hours each day for 14 days. The following items will be assessed at screening/baseline and at 30 minutes to 1 hour after patch removal on Days 8 ± 1 and 15 ± 1. • Presence of a chalazion by examination (clinical assessment) • [redacted] • Erythema of the chalazion site itself as measured by a 5-point scale (0 = no sign of erythema, 1 = slight erythema, 2 = mild erythema, 3 = moderate erythema, 4 = severe erythema) • Pain in study eyelid and eye of the study eyelid related to chalazion as measured by Visual Analog Scale (VAS) of 100 mm Patient Reported Outcome (PRO) will be assessed by a self-evaluation diary of chalazion (present or absent), completed daily by the subjects from Day 1 through Day 15 ± 1.
Sample Size	Approximately 260 subjects will be randomized.
Study Population	Male or female subjects aged ≥ 6 years with a chalazion
Inclusion Criteria	Subjects eligible to participate in the study must meet all of the following criteria: 1. Subjects aged ≥ 6 years of either sex and of any race. 2. Subjects with a diagnosis of a single chalazion with visible granuloma in the study eyelid. Study eyelid may be either an upper or lower eyelid. 3. Subjects with a chalazion with the granuloma area (height x width) ≤ 36 mm^2 when measured by a caliper. 4. Subjects with chalazion erythema score of ≥ 1 (as graded on a 5-point scale: 0 = no erythema, 1 = slight erythema, 2 = mild erythema, 3 = moderate erythema, 4 = severe erythema). 5. Chalazion intended for study treatment present for no more than 21 days based on patient history on Day 1. 6. Normal eyelid function without active signs of eye/eyelid infection in either eye.

	7. Must be willing and able to correctly apply and wear a transdermal patch to the eyelid for minimum of 16 hours and a maximum of 24 hours each day for the entire study treatment period, or have someone (guardian/caregiver) in the household who is willing and able to correctly apply a transdermal patch for the subject. 8. Female subjects must be 1-year postmenopausal, surgically sterilized or, if of childbearing potential, must have a negative urine pregnancy test on Day 1, and must agree to use a method of contraception for the entire study period. Approved methods of contraception include: abstinence, oral contraceptives, an intrauterine device (IUD) with spermicide, a female condom with spermicide, a diaphragm with spermicide, a cervical cap with spermicide, use of a condom with spermicide by sexual partner or a sterile sexual partner. 9. If male, subjects must be sterile or willing to use an approved method of contraception for the entire study period. Males must be willing to refrain from sperm donation for the entire study period. 10. Are able and willing to attend all study visits and follow all study-related instructions. 11. Have signed written informed consent before undergoing any study-related procedures and is willing to comply with all study procedures; or signed written consent from parent or legal guardian if the subject is a minor and signed written assent from subject, if appropriate. 12. Avoid wearing contact lenses in the study eye or using any new facial cosmetic products during the study period. 13. Avoid wearing any make-up, ointment, or moisturizer on the study eyelid where the study drug is applied (mascara on the eyelash is allowed) during the entire study period. 14. Ability to reliably report symptoms.
Exclusion Criteria	Subjects who meet the following criteria are not eligible to participate in this study: 1. Chalazion that has atypical features (a recurring chalazion at the same spot, abnormal surrounding lid tissue, associated loss of tissues). 2. History of chalazion incision and curettage in study eyelid. 3. Chalazion at the eyelid margin (≤ 2 mm distant from the edge of the study eyelid margin). 4. Multiple chalazia in the study eyelid or in any non-study eyelid(s). A single chalazion in any non-study eyelid(s) is(are) allowed. 5. Chalazion on the eyelid that was previously screen failed. Re-screening of the same subject is allowed only once. 6. Chalazion on the same eyelid or the opposing eyelid (i.e. same side) of the eyelid which was previously enrolled. Re-entry of the same subject is allowed only once. 7. Active ocular or eyelid infection (bacterial, viral, or fungal), or condition in the study eye/eyelid that in the investigator's opinion could affect the subject's health or the study parameters. 8. Presence of hordeolum in any one eyelid. 9. An abnormal skin condition on the study eyelid region (e.g., eczema, psoriasis, atopic dermatitis, etc.) where the study drug will be applied. 10. Intraocular pressure (IOP) greater than 22 mmHg in either eye. 11. Diagnosed with glaucoma in either eye. 12. History of steroid-induced elevation of IOP.

	13. Use of systemic (intravenous, intramuscular, oral), ophthalmic, or dermatological corticosteroids or immunosuppressant within 4 weeks prior to Day 1 and throughout the study period. Inhalant, intranasal, intra-articular, and perianal steroids are permitted. 14. Use of systemic or ophthalmic azithromycin in either eye within 5 weeks prior to Day 1 and throughout the study period, use of other systemic or ophthalmic macrolides (e.g. erythromycin, clarithromycin, etc.) in either eye within 2 weeks prior to Day 1 and throughout the study period, and use of tetracyclines (e.g. tetracycline, doxycycline, etc.) in either eye within 2 weeks prior to Day 1 and throughout the study period. 15. Use of periocular or intraocular corticosteroid injection or corticosteroid depot in either eye within 9 weeks prior to Day 1 and throughout the study period. 16. Female subjects who are pregnant or lactating. 17. Known allergy or sensitization to the test article or any formulation components. 18. History or evidence of ocular surgery in either eye or eyelid within the past 3 months. 19. History of refractive surgery in either eye within the past 6 months. 20. Planned surgery (ocular in either eye or eyelid or systemic) during the entire study period. 21. Participation in an investigational study within 30 days prior to Day 1. 22. Have any ocular condition in either eye that requires chronic use of topical ophthalmic medication (e.g., glaucoma, dry eye, allergic conjunctivitis) with exception of over-the-counter artificial tears or lubricant eye drops, anti-histamine drops, or that, in the investigator's opinion, supports the safe use of the study drug. 23. History of any previous functional or cosmetic eyelid surgery (including blepharopigmentation) in the study eyelid. 24. Any other condition that, in the opinion of the investigator, renders the subject unsuitable for study participation.
Dosage and Administration of Study Drug	This study will consist of up to 3 visits and one telephone contact occurring over a maximum 25-day period. Subjects (or the caregiver) will apply the study drug on the study eyelid daily in the clinic or at home after completing training at the site. Subjects will keep the study drug on the eyelid for a minimum of 16 hours and a maximum of 24 hours each day for 14 days. Gently cleanse the study eyelid and allow it to dry for approximately 30 minutes before applying a new study drug. On Days 8 ± 1 and 15 ± 1, the study drug should not be replaced with to a new study drug in the morning of the visit to ensure the study drug is worn for a minimum of 12 hours before removal by the investigator at the site. The subject may wear the study drug over 24 hours on these visit days if necessary. On Day 8 ± 1, subjects should apply a new study drug after completion of evaluations to ensure the study drug is worn for minimum of 16 hours on that day. The subject can then return to their normal schedule of study drug removal and replacement. Subjects will document time/date of each application and removal in the diary as well as any unusual events.
Efficacy Measures	The following items will be assessed at screening/baseline (Day 1), at 30 minutes to 1 hour after patch removal on Days 8 ± 1, and 15 ± 1. • Presence of a chalazion by examination (clinical assessment) • [redacted]

	• Erythema of the chalazion site itself as measured by the 5-point scale • Pain in study eyelid and the eye of the study eyelid related to chalazion as measured by VAS of 100 mm PRO will be assessed by self-evaluation diary of chalazion (present or absent), completed daily by the subjects from Day 1 through Day 15 ± 1. **Primary Outcome Measure:** Signs (Objective) • Complete Response (CR) of the study chalazion by Day 15 ± 1. Complete response is defined as the absence of any significant clinical signs of a chalazion, based on clinical judgment by an investigator. Scarring or skin defects resulting from healing of the chalazion are possible and allowed upon CR. [redacted] **Additional Secondary Outcome Measures**: Signs (Objective) • Change in size of the study chalazion from baseline to Days 8 ± 1 and 15 ± 1. • Change in erythema of the study chalazion from baseline to Days 8 ± 1 and 15 ± 1. Symptoms (Subjective) • Change in pain associated with the study chalazion in the study eye and eyelid assessed in VAS from baseline to Days 8 ± 1 and 15 ± 1.
Safety Measures	Adverse events (AEs) (observed or reported verbally or via diary) will be obtained following the first study drug application on Day 1 through Day 22 ± 3. The following assessments will be done in both eyes at baseline (pre-dose on Day 1), and after patch removal on Days 8 ± 1 and 15 ± 1. • Visual acuity (Snellen charts) • Slit-lamp biomicroscopy (lid, conjunctiva, cornea, anterior chamber and lens) • IOP measurement (Goldmann tonometer,Tono-Pen, or iCARE) Skin irritation of the TDS application site will be assessed in the study eyelid by the investigator at baseline (pre-dose on Day 1) and 30 minutes to 1 hour after patch removal by the study staff on Days 8 ± 1 and 15 ± 1 by using the 5-point Draize scale (0: No evidence of erythema, 1: Very slight erythema, 2: Well defined erythema, 3: Moderate to severe erythema, 4: Severe erythema [beet redness] to slight eschar formation [injuries in depth]).

Other Measures	• Patch adhesion will be assessed by the investigator prior to patch removal on Days 8 ± 1 and 15 ± 1 in the study eyelid only. (0: ≥ 90% adhered, 1: ≥ 75% to < 90% adhered, 2: ≥ 50% to < 75% adhered, 3: < 50% adhered, 4: patch completely off the skin). • Ocular and skin comfort query of the eye of the study eyelid and the study eyelid (comfort from study drug application) as measured in VAS of 100 mm length are to be conducted at baseline (Day 1 prior to study drug application), and prior to patch removal on Days 8 ± 1 and 15 ± 1. • Residual drug content of the used study drug collected at the site on Days 8 ± 1 and 15 ± 1 will be evaluated.
Study Duration	It is planned that each subject will participate in the study for a maximum of 25 days. Overall duration of the study will be approximately 10 months, depending on the rate of enrollment and number of subjects enrolled.
Study Centers	Up to 67 clinical sites

Table 1: Schedule of Events

[redacted]

[redacted]

[redacted]

1 INTRODUCTION

A chalazion, also known as a Meibomian gland lipogranuloma, is a cyst in the eyelid that is caused by a blocked Meibomian gland, in the upper or lower eyelid, that causes an inflammatory response. The Meibomian glands are responsible for excreting sebum and meibum that help lubricate the skin, eyelash hairs, and eyes. Chalazia are generally subacute dermal inflammations that are often uncomfortable and in rare cases can cause astigmatism that may require surgical treatment. Clinical signs and symptoms of a chalazion include swelling on the eyelid, eyelid tenderness, and irritation to the eye.

There are no current US FDA-approved products specifically to treat chalazion, however, typical treatments range from simple interventions, such as hot compresses, to more serious chalazion that require treatment with an injection of corticosteroid into edema or require surgical removal of the chalazion. Given no specific product is approved to target the chalazion in the eyelid subdermal region, off-label treatments with corticosteroid ophthalmic ointments and eye drops are common. These treatments often expose the eye to significant doses of corticosteroid and fail to adequately target the Meibomian gland, thus giving a less optimal effect and more risk of AEs like increase of IOP induced by steroid eye drops.

The anti-inflammatory and immunosuppressive effects of glucocorticoids, such as [redacted], rely on several molecular mechanisms, that have been elucidated by basic research (1). Three main mechanisms include direct effects on gene expression by the binding of glucocorticoid receptors to glucocorticoid-responsive elements (i.e., the induction of annexin I and mitogen-activated protein kinase phosphatase 1 [MKP-1]), indirect effects on gene expression through the interactions of glucocorticoid receptors with other transcription factors (i.e., NF-*k*B and activator protein 1), and glucocorticoid receptor–mediated effects on second-messenger cascades (i.e., the PI3K–Akt–eNOS pathway). Unfortunately, because some of these mechanisms are also involved in systemic physiologic signaling rather than inflammatory signaling, the therapeutic effects of systemic glucocorticoids in inflammation are often accompanied by clinically significant side effects when given in the systemic circulation. Given that the target indication is a chalazion, targeting the application of [redacted] to the site of inflammation is considered the most effective approach with the least potential for systemic or ocular side effects.

The SUN-131 ([redacted]) TDS is designed for local delivery of a corticosteroid, [redacted], to the upper or lower eyelid. This TDS is specially engineered to gently adhere to the eyelid and is shaped to fit the contours of the eye. The backing and adhesives used are also designed to allow removal of the patch without causing irritation and to be flexible for adequate comfort. Thus, targeted local delivery of [redacted] to treat the chalazion can be achieved from this unique transdermal design without significant exposure of the active agent to the eye, as with ointment or drops. Thus, this is considered a dermal application of a

TDS to treat a local extra-ocular disease in the eyelid. The low local dose also will minimize any potential for systemic exposure and minimize exposure to the eye.

[redacted]

1.1 Phase 1 Clinical Evaluation of the SUN-131 TDS:

The safety and performance of the SUN-131 TDS was assessed in a single-center, randomized, double-masked, placebo-controlled Phase 1 clinical trial that included 2 parts. Part 1 evaluated a single dose application of SUN-131 TDS at 3 concentrations to evaluate safety and tolerability as compared to placebo. Part 2 evaluated multiple-dose administration of 2 concentrations SUN-131 TDS for 14 consecutive days as compared to placebo TDS.

In Part 1, adult healthy subjects were randomly assigned to receive one of the following study drug doses on both upper and lower eyelids in the right or left eye:

- SUN-131 0.2% TDS (n = 8)
- SUN-131 0.7% TDS (n = 8)
- SUN-131 1.5% TDS (n = 8)
- Placebo TDS (contralateral eye for each subject, n = 24)

Each subject was randomized to wear 2 active patches on the upper and lower eyelids of the right or left eye. Two placebo patches were worn on the upper and lower eyelid of the contralateral eye. Thus, a total of 4 patches were administered, with 2 active and 2 placebo patches on each eye. All patches were worn for 24 hours (e.g., 08:00 to 08:00 the following day). Given that clinically significant systemic levels of [redacted] were not expected after single application of the SUN-131 TDS, and the safety of topical clobetasol propionate creams with greater anticipated exposure did not lead to significant plasma levels, pharmacokinetic sampling was not conducted in this initial safety assessment.

In Part 2 of the study, the 2 highest strength concentrations of the SUN-131 TDS (i.e. 0.7% and 1.5%) were chosen for further evaluation through multiple-dose application. Adult healthy subjects were randomized to wear one active patch on either the upper or lower eyelid of the right or left eye daily for 14 days. A placebo patch was worn on the contralateral eyelid in the same location. The SUN-131 TDS concentrations planned for this study were:

- SUN-131 0.7% TDS (n = 8)
- SUN-131 1.5% TDS (n = 8)

- Placebo TDS (contralateral eye for each subject, n = 16)

All patches were worn for 16 ± 2 hours (approximately 16:00 to 08:00 the following day). Subjects were retained in the clinic overnight on Days 1 and 14 of this study for evaluation and pharmacokinetic sampling. Subjects on Day 1 had their patches applied by trained study personnel at the site and they were instructed on the proper technique to apply the patch at home. Limited pharmacokinetic sampling was taken prior to dosing and approximately 8, 12, and 16 hours after patch application on Days 1 and 2. On Day 14, the subject again had the patches applied by study personnel for the final day of evaluation and pharmacokinetic sampling. Pharmacokinetic sampling for Days 14 and 15 included plasma samples taken prior to dosing and approximately 8, 12, 16, and 24 hours after patch application.

In Part 1 (single-application) of this study a total of 24 subjects enrolled and received study drug and were included in the safety analysis data set for the single application. All 24 subjects who initiated the scheduled single application in Part 1 completed the study and there were no missed doses of study medication. Eleven of the dosed subjects enrolled in the single application portion of this study (Part 1) were Black (11 of 24 subjects, 45.8%), 9 were White (9 of 24 subjects, 37.5%), and 4 were Asian (4 of 24 subjects, 16.7%). Subjects ranged in age from 23 to 65 years. Among these subjects were 54.2% (13 of 24) were male and 45.8% (11 of 24) were female.

In Part 2 of this study a total of 16 subjects enrolled and received study drug and were included in the safety analysis data set for repeated application. A total of 16 subjects who initiated the scheduled repeated application in Part 2 completed the study and there were no missed doses of study medication. Seven (7) of the dosed subjects enrolled in the repeated application portion of this study (Part 2) were Black (7 of 16 subjects, 43.8%), 7 were White (7 of 16 subjects, 43.8%), and 2 were Asian (2 of 16 subjects, 12.5%). Subjects ranged in age from 24 to 58 years. Among these subjects, 18.8% (3 of 16) were male and 81.3% (13 of 16) were female. There were no statistically significant imbalances in baseline characteristics across groups in the trial.

In the SUN-131 0.7% TDS group most subjects (5 of 8) demonstrated systemic exposure to [redacted] below the limit of quantification (< 10.0 pg/mL) of the liquid chromatography-mass spectrometry (LC/MS-MS) bioanalytical method. One subject (R24103) had detectable, but low, levels of [redacted] in plasma after 12 hours (10.1 pg/mL) and 16 hours (13.5 pg/mL) on Day 1. Three subjects (R24101, R24103, and R24107) had detectable levels ranging from 10.5 pg/mL to 15.8 pg/mL on Day 14 with the peak plasma levels observed in all cases at 16 hours after patch application.

In the SUN-131 1.5% TDS group, all subjects demonstrated at least low level systemic exposure to [redacted]. Six (6) of 8 subjects had plasma levels of between 10.1 and 19.1 pg/mL on Day 1 with the peak plasma levels usually occurring after 16 hours. Four (4) of 8 subjects (R25102, R25103, R25105, and R25107) had plasma levels between 11.0 and 17.3 pg/mL on Day 14 with peak levels around 16 hours. One subject, who did not demonstrate

systemic levels of exposure through 16 hours on Day 14, demonstrated a low level of [redacted] exposure (10.5 pg/mL) at 24 hours after patch application on Day 14.

The systemic exposure to [redacted] was very low throughout the study. While detectable levels of [redacted] (> 10.0 pg/mL) could be found, these levels generally were less than 20 pg/mL, which is approximately 30- to 790-fold lower than the exposure after application of [redacted] reported in the literature. There was no indication of accumulation with repeat application of the SUN-131 TDS.

SUN-131 TDS exhibited excellent adhesion in both the single application and multiple application dose groups. In the multiple application dose groups where subjects self-administered the SUN-131 TDS at home for 12 of 14 days, of all patches administered there were 2 events (0.4% of patch applications) where there was complete patch detachment. This includes a fall-off of a placebo TDS on Day 2 and a SUN-131 0.7% TDS on Day 2. There were 5 events of slight lifting of the study drug (score 1: < 25%) reported, of which 4 of these events were in the placebo group. There were 2 event of moderate lifting (score 2: 25% to 50%) with one in the SUN-131 1.5% TDS group on Day 15 and one in the SUN-131 1.5% TDS group on Day 4. Overall, there were 224 applications of SUN-131 TDS in the multiple administration groups (Part 2) of which there was 1 event (0.45% of applications) of fall-off, 2 events (0.9% of applications) of moderate lifting (25% to 50% lifted), and 1 event (0.45% of applications) of slight lifting (< 25%) of the patch. In comparison, there were 224 applications of placebo TDS in the multiple administration groups (Part 2) of which there was 1 event (0.45% of applications) of fall-off and 4 events (1.8% of applications) of slight lifting (< 25%) of the placebo patch.

Overall, 1 of 24 subjects (4.2%) in the single application treatment portion of the trial (Part 1) reported at least 1 treatment emergent adverse event (TEAE). The TEAE was considered mild (1 event, 4.2%) in severity. No subjects experienced TEAEs that were considered at least possibly treatment-related by the investigator. The highest percentage of subject-reported TEAEs was classified in the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) of Eye disorders (4.2%).

Across treatment groups in the single application portion of the study (Part 1), the highest percentage of TEAEs were in the SUN-131 0.2% TDS (1 subject, 12.5%). There were no subjects who experienced a TEAE that was considered even possibly related to study medication. There were no TEAEs that were severe and no SAEs occurred in the single application portion of the study.

Overall, 3 of 16 subjects (18.8%) in the repeated application treatment groups reported at least 1 TEAE. There was a total of 5 TEAEs reports in the 3 subjects who experienced an event. A total of 1 of 16 subjects (6.3%) experienced a TEAE (eye pain) that was considered at least possibly treatment-related by the investigator. The highest percentage of subjects reported TEAEs classified in the SOC of Nervous system disorders (3 events of headache: 18.8%),

followed by Eye disorders (1 event of eye pain: 6.3%) and Musculoskeletal and connective tissue disorders (1 event of neck pain: 6.3%).

Across treatment groups in the repeated application, the highest percentage of TEAEs were in the SUN-131 0.7% TDS group (2 subjects, 25.0%), and the SUN-131 1.5% TDS group (1 subject, 12.5%).

Among events that were considered at least possibly related in the repeated application treatment, there was 1 subject (6.3%) who experienced a related TEAE (eye pain) in the SUN-131 0.7% TDS group. There were no events in the SUN-131 1.5% TDS group that were considered possibly related to study medication. There were no TEAEs that were severe and no SAEs occurred in the single application portion of the study.

There were no notable findings or changes in safety assessments including visual acuity (VA), slit-lamp biomicroscopy, IOP, skin irritation, or tolerability assessed by ocular and skin comfort questionnaires.

Overall, the SUN-131 TDS appeared to deliver adequate drug amounts to the eyelid without notable side effects, skin irritation, skin discomfort or other safety concerns. The performance of the SUN-131 TDS with regards to adhesion and drug delivery was considered excellent. The systemic exposure to [redacted] was well below levels considered safe after administration of topical [redacted]

1.2 Phase 2 Clinical Evaluation of the SUN-131 TDS:

Senju has more recently completed a Phase 2, multi-center, randomized, placebo-controlled clinical trial in adult subjects with a chalazion. Subjects were randomly assigned to receive either SUN-131 1.5% TDS or placebo TDS in a 1:1 ratio. All patches were worn for 16 ± 4 hours each day for 21 days. A total of 69 subjects were enrolled in the trial and 58 completed the trial. There were 11 subjects, 6 in the SUN-131 1.5% TDS group and 5 in the placebo TDS group, who discontinued the study for non-safety-related reasons. Of the 69 subjects enrolled, 68 received either the SUN-131 1.5 % TDS or the placebo TDS and thus were evaluable for safety. A total of 35 subjects received at least one dose of active SUN-131 1.5% TDS, of which 29 subjects completed the study with all doses through Day 21. A total of 33 subjects received at least one dose of placebo TDS of which 29 subjects completed the study with all doses through Day 21.

Overall, the safety of the SUN-131 1.5% TDS was excellent with no clinically meaningful product-related adverse effects. There were no notable changes in VA, slit-lamp biomicroscopy, IOP, skin irritation or ocular and skin discomfort. Twenty-four (24) of 68 subjects (35.3%) experienced at least 1 TEAE in the study. Eight (8) subjects (11.8%) experienced TEAEs that were considered treatment-related by the investigator. The most frequently experienced TEAEs overall in the study were chalazion (3 subjects; 4.4%) and eye pruritus (3 subjects, 4.4%). Thus, the SUN-131 1.5% TDS demonstrated a good safety profile for the intended indication.

2 STUDY OBJECTIVES

To evaluate the efficacy and safety of SUN-131 1.5% TDS as compared with placebo TDS in the treatment of chalazion based on the proportion of subjects who have CR. Complete response is defined as the absence of any significant clinical signs of a chalazion, based on clinical judgment by an investigator, with possible scarring or skin defects resulting from healing of the chalazion allowed**.**

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a multi-center, double-masked, randomized, placebo-controlled evaluation of the safety and efficacy of SUN-131 1.5% TDS as compared to placebo TDS in subjects with a chalazion. Subjects who may be enrolled will have only one eyelid having a single chalazion with a single visible granuloma, and its size ≤ 36 mm^2 and erythema scale score ≥ 1.

Subjects meeting all inclusion and exclusion criteria will be centrally randomly assigned to receive one of the following treatments in the affected eyelid:

- SUN-131 1.5% TDS (n = 130)
- Placebo TDS (n = 130)

The randomization will be stratified by age group (<12 years, ≥12 years).

Subjects will be trained to apply the placebo TDS during screening. Subjects (or the guardian/caregiver) will apply the study drug on the study eyelid daily for 14 days. At baseline prior to application of the study drug, subjects will be assessed in both eyes for VA, slit-lamp biomicroscopy, IOP measurement, skin and ocular comfort query of the study eyelid and eye of the study eyelid, and skin irritation of study drug application site separate from the chalazion on the study eyelid. The chalazion site itself will also be assessed for erythema, pain related to the

chalazion, and the size of the chalazion by measuring the height and width of the chalazion with a caliper. A photograph of the chalazion at baseline will also be taken prior to first application of the study drug.

On Day 1, the subject may apply the first study drug in the clinic or at home depending on the anticipated schedule for study drug application for the entire treatment period. On Days 8 ± 1 and 15 ± 1, the study drug should not be replaced with a new study drug in the morning of the visit to ensure the study drug is worn for minimum of 12 hours before removal by the investigator at the site. The subject may wear the study drug over 24 hours on these visit days if necessary. On Day 8 ± 1, subjects should apply a new study drug after completion of evaluations to ensure the study drug is worn for minimum of 16 hours on that day. The subject can then return to their normal schedule of study drug removal and replacement.

All subjects will return to the site on Days 8 ± 1 and 15 ± 1 for evaluations. Subjects should not remove their patch on Days 8 ± 1 and 15 ± 1 prior to the clinic visit. During these visits, the subject will complete the ocular/skin comfort query for the study eyelid and eye of the study eyelid prior to removal of the patch. The study drug will then be removed by the investigator to assess the level of skin irritation of the study eyelid associated with the study drug. Adverse events, concomitant medication use, and therapy are queried. Ocular safety examinations including VA, slit-lamp biomicroscopy, and IOP measurement will be performed in both eyes. A clinical evaluation will also be performed to determine if the chalazion is still present. If the chalazion is still present, the chalazion site will also be assessed for erythema of the chalazion site itself, pain related to the chalazion in the study eyelid and eye of the study eyelid, and the size of the chalazion by measuring the height and width of the chalazion with a caliper. Subjects will provide daily self-evaluation of the study chalazion from Day 1 through Day 15.

On Day 22 ± 3, the subject will be contacted by telephone to obtain AEs and any concomitant medications and therapy taken since the last visit.

There will be no safety data monitoring, nor any special steering or evaluation committees for this study. Data review and safety assessments will be conducted by the medical monitor periodically throughout the trial and at the study conclusion.

3.2 Rationale of the Study Design

This is a prospective multi-center, double-masked, randomized, placebo-controlled clinical trial. Subjects will be centrally randomly assigned in 1:1 ratio to receive either a SUN-131 1.5% TDS or placebo TDS on the eyelid affected by the chalazion. The primary purpose of the study is to evaluate the efficacy and safety of the SUN-131 1.5% TDS as compared with placebo TDS in the treatment of chalazion.

The use of a placebo TDS as the control allows for the proper assessment of efficacy and any ocular or dermal irritation due to the study drug materials or adhesive, as opposed to the active SUN-131 1.5% TDS.

3.3 Duration of Application Exposure

SUN-131 1.5% TDS or placebo TDS will be applied for a minimum of 16 hours and a maximum of 24 hours each day for 14 days. On Day 8 ± 1, subjects may apply a new study drug after completion of evaluations to ensure the study drug is worn for a minimum of 16 hours each day. On Days 8 ± 1 and 15 ± 1, the study drug should not be replaced with a new study drug in the morning of the visit to ensure the study drug is worn for a minimum of 12 hours before removal by the investigator at the site. The subject may wear the study drug over 24 hours on these visit days if necessary. On Day 8 ± 1, subjects should apply a new study drug after completion of evaluations to ensure the study drug is worn for minimum of 16 hours on that day. The subject can then return to their normal schedule of study drug removal and replacement. Dosing should not be discontinued unless there is an AE that warrants stopping treatment. If the absence of the chalazion is observed prior to Day 14, dosing should be continued until Day 14 to ensure complete resolution of the chalazion. Complete response is defined as the absence of any significant clinical signs of a chalazion with possible scarring or skin defects resulting from healing of the chalazion allowed.

3.4 Schedule of Assessments

3.4.1 Visit 1 (Screening /Baseline: Day 1)

Subjects will sign an ICF prior to any study-specific procedures (note: Standard of Care [SoC] assessments may be done prior to signing the ICF and incorporated into the study if within the allowed screening process). Where appropriate, study subjects who are < 18 years of age should assent to enroll in the study (with age of assent to be determined by the IRB and be consistent with local legal requirements). Demographics, medical and ocular history, and any concomitant medication and therapy use will be documented. The ocular history will include any previously diagnosed ophthalmic abnormalities and ocular surgeries (including laser procedures). The subject, if female, will be tested to confirm she is not pregnant using an in-house US FDA-approved home urine pregnancy test. The presence of a chalazion will be confirmed as well as the size of the chalazion, erythema of the chalazion itself, and pain related to chalazion in the study eyelid and eye of the study eyelid as part of the screening procedure. A photograph of the chalazion at baseline will also be taken prior to first study drug application. Subjects will also be trained on study drug application at baseline to confirm their ability to apply the patch at home. Training with training patches should only be conducted on the non-study eyelids. When considering enrollment of younger children, and the chalazion is on the upper eyelid, the eyelid size with the eyes closed should be evaluated and ensure that the study drug can be applied securely.

Ocular safety examinations including VA, slit-lamp biomicroscopy, and IOP measurement in both eyes, skin irritation assessment of the skin around the chalazion, size of chalazion, erythema of the chalazion itself, pain related to chalazion, and ocular/skin comfort query of the study eyelid/eye will be obtained at baseline prior to the application of the first study drug. Concomitant medications will also be evaluated at baseline. Adverse events will be evaluated following the first study drug application on Day 1. First study drug application may be done at the site or by the subject/caregiver at home depending on the anticipated dosing schedule.

Subjects meeting all inclusion criteria and none of the exclusion criteria will be enrolled into the study. Training will be conducted on study procedures and on the appropriate method to apply and remove the study drug. Subjects will be centrally randomly assigned in a 1:1 ratio to receive SUN-131 1.5% TDS or placebo TDS applied to the study eyelid affected by the chalazion. The randomization will be stratified by age group (<12 years, ≥12 years). Subjects will receive a 1-week supply of study drug, including backup study drug, and be instructed to wear the study drug daily for a minimum of 16 hours and a maximum of 24 hours, and gently cleanse and wipe the study eyelid and to allow it to dry for approximately 30 minutes before applying a new study drug.
Subjects will continue to apply the study drug each day on the study eyelid for the full treatment period. Subjects will record the time of study drug application, study drug removal, and any unusual events or patch adhesion issues in a daily subject diary, as well as any missed/fall-off/misapplications. Subjects will keep all used and unused study drug in a provided container and return to the sites.

3.4.2 Visits 2-3 (Treatment Period: Days 8 ± 1 and 15 ± 1)

Subjects will return to the study site on Days 8 ± 1 and 15 ± 1 prior to removal of the patch from Days 7 ± 1 and 14 ± 1. On Days 8 ± 1 and 15 ± 1, the study drug should not be replaced with a new study drug in the morning of the visit to ensure the study drug is worn for a minimum of 12 hours before removal by the investigator at the site. The subject may wear the study drug over 24 hours on these visit days if necessary. On Day 8 ± 1, subjects should apply a new study drug after completion of evaluations to ensure the study drug is worn for a minimum of 16 hours on that day. The subject can then return to their normal schedule of study drug removal and replacement. Subjects will be queried for AEs and concomitant medication use and therapy. Study drug accountability is done by collecting all of the used and unused study drug and reviewing the subject diary. Prior to removal of the patch the investigator will evaluate the patch adhesion. The investigator will remove the study drug and assess the level of skin irritation of the eyelid where the study drug was placed, excluding the site of the chalazion. The removed study drug will be placed in a provided container and retained for collection by Senju. The subject will complete an ocular and skin comfort query of the study eyelid and eye of the study eyelid. Ocular examinations for safety will be performed in both eyes, including VA, slit-lamp biomicroscopy, and IOP measurement.

The investigator will also evaluate if the study chalazion is still present. If the study chalazion is still present, erythema associated with the chalazion site itself will be assessed, the subject will be asked to assess the pain associated with the chalazion, and the size of the chalazion will be evaluated ([redacted]). If the investigator judges that the chalazion is not present, other evaluations of chalazion (size, pain, and erythema) will not be not performed. Evaluation of the chalazion should be done by the same investigator as much as possible.

Subjects will be provided with another 1-week supply of study drug including backup study drug on Day 8 ± 1. Subjects will return the subject diary on Day 15 ± 1.

See the section on Early Exit Procedures in handling of early termination.

3.4.3 Telephone Contact (Follow-Up: Day 22 ± 3)

Subjects will be contacted by telephone on Day 22 ± 3 and will be queried for AEs and concomitant medication and therapy use.

3.5 Outcome Measures

The following items will be assessed at screening/baseline (Day 1), and at 30 minutes and 1 hour after patch removal on Days 8 ± 1 and 15 ± 1.

- Presence of a chalazion by examination (clinical assessment)
[redacted]
- Erythema of the chalazion site itself
- Pain related to chalazion in the study eyelid and eye of the study eyelid
- Presence of a chalazion (daily patient reported outcome)

3.5.1 Primary Outcome Measure

- CR of the study chalazion by Day 15 ± 1. Complete response is defined as the absence of any significant clinical signs of a chalazion, based on clinical judgment by an investigator. Scarring or skin defects resulting from healing of the chalazion are possible and allowed upon CR.

The assessment of CR should be done by the same investigator as much as possible.

3.5.2 Key Secondary Outcome Measures

[redacted]

3.5.3 Additional Secondary Outcome Measures

- Change in size of the chalazion from baseline to Days 8 ± 1 and 15 ± 1. Size of the chalazion will be assessed using a caliper provided for the study and measured as height and width in mm. [redacted] See Section 5.7 for full-scale information.
- Change in erythema of the study chalazion from baseline to Days 8 ± 1 and 15 ± 1. Erythema of the chalazion site itself will be assessed using a 5-point scale (i.e., 0 = no erythema to 4 = severe erythema). See Section 5.8 for full-scale information.
- Change in pain associated with the study chalazion in the study eyelid and eye of the study eyelid assessed in VAS from baseline to Days 8 ± 1 and 15 ± 1. Pain associated with the chalazion in the study eye and eyelid will be assessed at baseline (pre-dose on Day 1), and on Days 8 ± 1 and 15 ± 1. Pain assessments will be done at the clinical site using a 100 mm VAS. See Section 5.9 for full-scale information.

The assessment of the chalazion should be done by the same investigator as much as possible throughout the study period.

3.5.4 Safety Analysis

Safety assessments for this study include:

- Adverse events (observed or reported verbally or via diary) will be obtained following first study drug application on Day 1 though the follow-up period on Day 22 ± 3.
- Ocular safety: The following assessments will be done in both eyes at baseline (pre-dose on Day 1) and after patch removal on Days 8 ± 1 and 15 ± 1:
    - Visual acuity (Snellen chart)
    - Slit-lamp biomicroscopy (lid, conjunctiva, cornea, anterior chamber and lens)
    - IOP measurement (Goldmann tonometer,Tono-Pen, or iCARE)
- Skin irritation (from study drug): Skin irritation of the study drug application site will be assessed by the investigator at baseline (pre-dose on Day 1), and after patch removal on Days 8 ± 1 and 15 ± 1. On Days 8 ± 1 and 15 ± 1 assessments will be conducted 30 minutes to 1 hour after patch removal by the study staff in the clinic. Skin irritation is evaluated based on a 5 point Draize scale, where 0 = no evidence of erythema to 4 = severe erythema (beet redness) to slight eschar formation (injuries in depth). See Section 5.3 for full details of the scale. Skin irritation should be assessed by the same investigator and the same time of the day throughout the study period as much as possible.

3.5.5 Other Measures

- Tolerability: Ocular and skin comfort will be assessed in eye of the study eyelid and the study eyelid on Day 1 prior to study drug application and prior to patch removal on Days 8 ± 1 and 15 ± 1 using the following scales (See Section 5.2 for full details). Subjects will be assessed the following questions:
    - Ocular comfort query in eye of the study eyelid (VAS with 0 mm = very comfortable and 100 mm = very uncomfortable)
    - Skin comfort query in the study eyelid (VAS with 0 mm = very comfortable and 100 mm = very uncomfortable)
- Patch adhesion: will be assessed in the study eyelid only prior to patch removal on Days 8 ± 1 and 15 ± 1. Scale is provided in Section 5.4 and is scored as 0: ≥ 90% adhered, 1: ≥ 75% to < 90% adhered, 2: ≥ 50% to < 75% adhered, 3: < 50% adhered, 4: patch detached (patch completely off the skin). This assessment should be done by the same investigator and at the same time of the day throughout the study period as much as possible.
- Residual drug content: will be measured from the used study drug removed by the investigator and collected at the site on Days 8 ± 1 and 15 ± 1.

4 DISCUSSION OF STUDY DESIGN

[redacted]

4.1 Selection of Study Population

Male or female subjects aged ≥ 6 years with a chalazion will be selected for this study.

4.1.1 Inclusion Criteria

Subjects eligible to participate in the study must meet all of the following criteria:

1. Subjects aged ≥ 6 years of either sex and of any race
2. Subjects with a diagnosis of a single chalazion with visible granuloma in the study eyelid. Study eyelid may be either an upper or lower eyelid.
3. Subjects with a chalazion with the granuloma area (height x width) ≤ 36 mm^2 when measured by a caliper.
4. Subjects with chalazion erythema score of ≥ 1 (as graded on a 5-point scale: 0 = no signs of erythema, 1 = slight erythema, 2 = mild erythema, 3 = moderate erythema, 4 = severe erythema).
5. Chalazion intended for study treatment present for no more than 21 days based on patient history on Day 1.
6. Normal eyelid function without active signs of eye and eyelid infection in either eye.
7. Must be willing and able to correctly apply and wear a transdermal patch to the eyelid for minimum of 16 hours and maximum of 24 hours each day for the entire study treatment period, or have someone (guardian/caregiver) in the household who is willing and able to correctly apply the transdermal patch for the subject.
8. Female subjects must be 1-year postmenopausal, surgically sterilized, or women of childbearing potential must have a negative urine pregnancy test on Day 1, and must agree to use a method of contraception for the entire study period. Approved methods of contraception include: abstinence, oral contraceptives, an IUD with spermicide, a female condom with spermicide, a diaphragm with spermicide, a cervical cap with spermicide, use of a condom with spermicide by sexual partner, or a sterile sexual partner.
9. If male, subjects must be sterile or willing to use an approved method of contraception for the entire study period. Males must be willing to refrain from sperm donation for the entire study period.
10. Are able and willing to attend all study visits and follow all study-related instructions.
11. Have signed written informed consent before undergoing any study-related procedures and is willing to comply with all study procedures; or signed written consent from parent or legal guardian if the subject is a minor and signed written assent from subject, if appropriate.
12. Avoid wearing contact lenses in the study eye or using any new facial cosmetic products during the study period.
13. Avoid wearing any make-up, ointment, moisturizer on the study eyelid where the study drug is applied (mascara on the eyelash is allowed) during the entire study period.
14. Ability to reliably report symptoms.

4.1.2 Exclusion Criteria

Subjects who meet the following criteria are not eligible to participate in this study:

1. Chalazion that has atypical features (a recurring chalazion at the same spot, abnormal surrounding lid tissue, associated loss of tissues).
2. History of chalazion incision and curettage in study eyelid.
3. Chalazion at the eyelid margin (≤ 2 mm distant from the edge of the study eyelid margin).
4. Multiple chalazia in the study eyelid or in any non-study eyelid(s). A single chalazion in any non-study eyelid(s) is(are) allowed. .
5. Chalazion on an eyelid that was previously screen failed. Re-screening of the same subject is allowed only once.
6. Chalazion on the opposing eyelid (i.e. same side) of an eyelid which was previously enrolled. Re-entry of the same subject is allowed only once.
7. Active ocular or eyelid infection (bacterial, viral, or fungal), any ocular or eyelid condition in the study eyelid/eye of study eyelid that in the investigator's opinion could affect the subject's health or the study parameters.
8. Presence of hordeolum in any one eyelid.
9. An abnormal skin condition on the study eyelid region (e.g., eczema, psoriasis, atopic dermatitis, etc.) where the study drug will be applied.
10. Intraocular pressure greater than 22 mmHg in either eye.
11. Diagnosed with glaucoma in either eye.
12. History of steroid-induced elevation of IOP.
13. Use of systemic (intravenous, intramuscular, oral), ophthalmic, or dermatological corticosteroids or immunosuppressant within 4 weeks prior to Day 1 and throughout the study period. Inhalant, intranasal intra-articular, and perianal steroids are permitted.
14. Use of systemic or ophthalmic azithromycin in either eye within 5 weeks prior to Day 1 and throughout the study period, use of other systemic or ophthalmic macrolides (e.g. erythromycin, clarithromycin, etc.) in either eye within 2 weeks prior to Day 1 and

throughout the study period, and use of tetracyclines (e.g. tetracyclines, doxycyclines, etc.) in either eye within 2 weeks prior to Day 1 and throughout the study period.

15. Use of periocular or intraocular corticosteroid injection or corticosteroid depot in either eye within 9 weeks prior to Day 1 and throughout the study period.
16. Female subjects who are pregnant or lactating.
17. Known allergy or sensitization to the test article or any formulation components.
18. History or evidence of ocular surgery in either eye or eyelid within the past 3 months.
19. History of refractive surgery in the either eye within the past 6 months.
20. Planned surgery (ocular in either eye or eyelid or systemic) during the entire study period.
21. Participation in an investigational study within 30 days prior to Day 1.
22. Have any ocular condition in either eye that requires chronic use of topical ophthalmic medications (e.g., glaucoma, dry eye, allergic conjunctivitis) with exception of over-the-counter artificial tears or lubricant eye drops, anti-histamine drops, or that, in the investigator's opinion, supports the safe use of the study drug.
23. History of any previous functional or cosmetic eyelid surgery (including blepharopigmentation) in the study eyelid.
24. Any other condition that, in the opinion of the investigator, renders the subject unsuitable for study participation.

4.1.3 Removal of Subjects from Treatment or Assessment

Subjects may withdraw their consent to participate in this study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn. **The medical monitor must be notified of all subject withdrawals within 24 hours by telephone or email.**

In addition, the investigator may withdraw a subject from the study for any of the following reasons:

- A protocol violation occurs,
- The subject is lost to follow-up,
- A serious or intolerable AE occurs, or
- The sponsor or investigator terminates the study.

The sponsor may withdraw a subject for noncompliance with use of study medication if they do not apply the study drug for a minimum of 16 hours and a maximum of 24 hours for at least 80% of the time required (or at least 5 days per week) and miss more than 2 of 7 days of application in the trial. Senju also reserves the right to discontinue the study at any time for either clinical or administrative reasons.

If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. If the subject cannot be reached by telephone after 2 attempts, a certified letter should be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the investigator. Attempts to contact the subject should be documented in the study records.

Prior to enrollment into the study, the investigator or designee must explain to each subject that the subject's protected health information obtained during the study may be shared with the study sponsor, regulatory agencies, and the IRB or EC in order to analyze and evaluate study results. It is the investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations. If permission to use protected health information is withdrawn, it is the investigator's responsibility to obtain a written request, as well as to ensure that no further data will be collected from the subject and the subject will be removed from the study.

4.1.4 Subject Identification

Each subject will be assigned a unique subject identifier. This unique identifier will be shown on all electronic Case Report Form (eCRF) pages within the Electronic Data Capture (EDC) system.

4.1.5 Early Exit Procedures

In the event of an early withdrawal of a subject the following procedures should be followed.

- If voluntary withdrawal from the trial, the subject will be asked to complete all final visit assessments (Early Termination Visit Assessment).
    - If the subject does not agree and withdraws consent, only data up to the time that the subject has withdrawn consent may be used and no other assessments should be performed. If SoC evaluations are required for safety reasons these may be conducted with consent of the subject.
    - If the subject agrees to have assessments prior to exiting the study and withdrawing consent, the subject will receive all assessments listed in Early Termination of the Schedule of Events.

4.2 Treatments

4.2.1 Treatments Administered

This study will consist of up to 3 visits and one telephone contact occurring over a maximum 25-day period. Subjects (or the caregiver) will apply the first study drug to the study eyelid on Day 1 either in the clinic or at home after completing training at the site. Subjects will wear the study drug for a minimum 16 hours and a maximum of 24 hours each day for 14 days. Gently cleanse the study eyelid and allow it to dry for 30 minutes before applying a new study drug. Ideally, the study drug will be applied and removed at the same times each day. On Days 8 ± 1 and 15 ± 1, the study drug should not be replaced with a new study drug in the morning of the visit to ensure the study drug is worn for a minimum of 12 hours before removal by the investigator at the site. The subject may wear the study drug over 24 hours on these visit days if necessary. On Day 8 ± 1, subjects should apply a new study drug after completion of evaluations to ensure the study drug is worn for a minimum of 16 hours on that day. The subject can then return to their normal schedule of study drug removal and replacement. Efficacy assessment and ocular and skin measures (safety and tolerability) will be conducted at Day 1, and Days 8 ± 1 and 15 ± 1.

4.3 Product Characteristics

SUN-131 1.5% TDS is [redacted]

[redacted]

The SUN-131 1.5% TDS will be provided [redacted]

4.3.1 Storage and Labeling

At the study site, all study drugs must be stored under the conditions specified in the Investigator's Brochure in a secure area accessible only to the designated pharmacists and study site personnel. All study drugs must be stored and inventoried, and the inventories carefully and

accurately documented according to applicable state, federal and local regulations, ICH GCP, and study procedures.

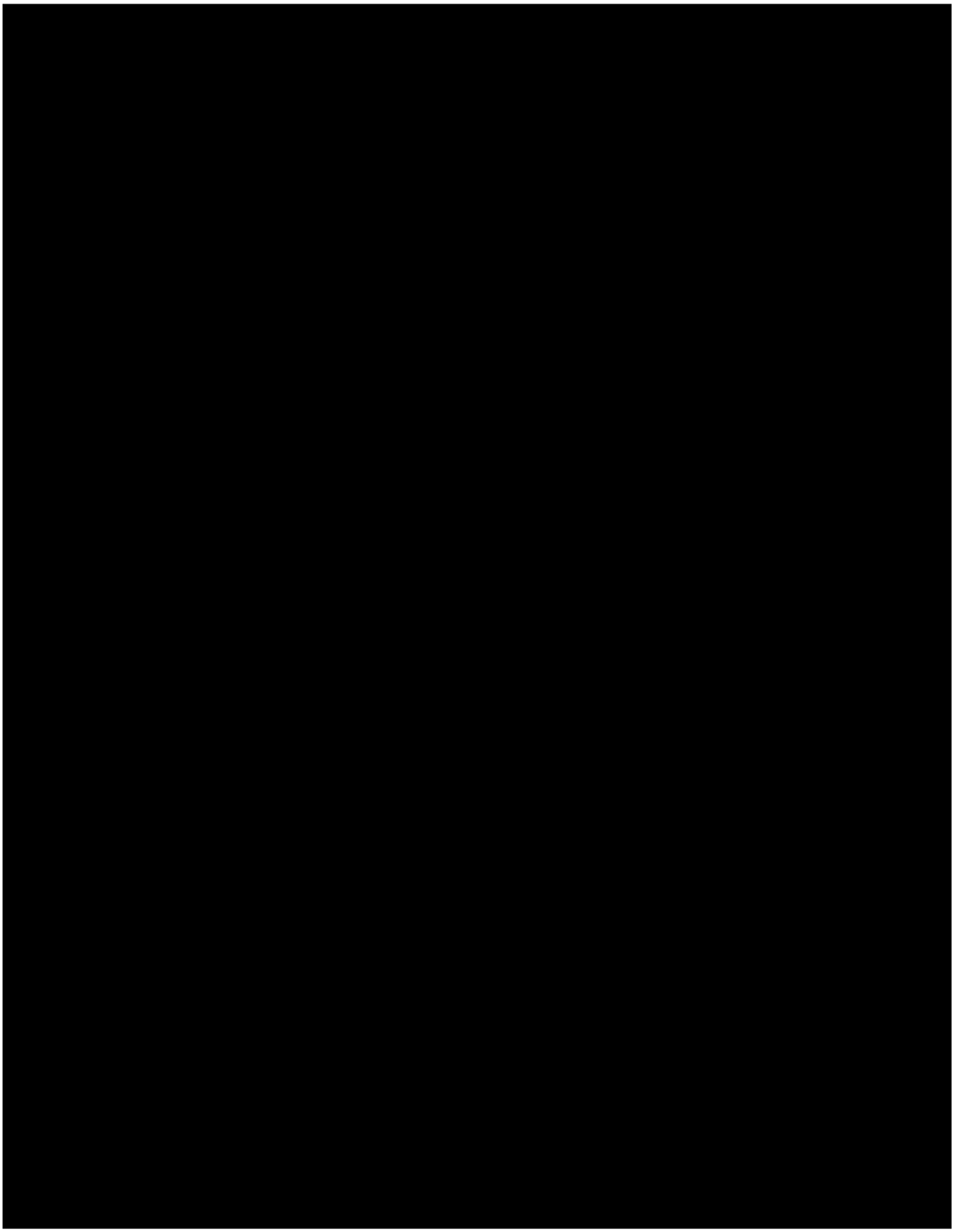
The study drug should be stored at 15°C to 25°C, protected from freezing and exposure to light.

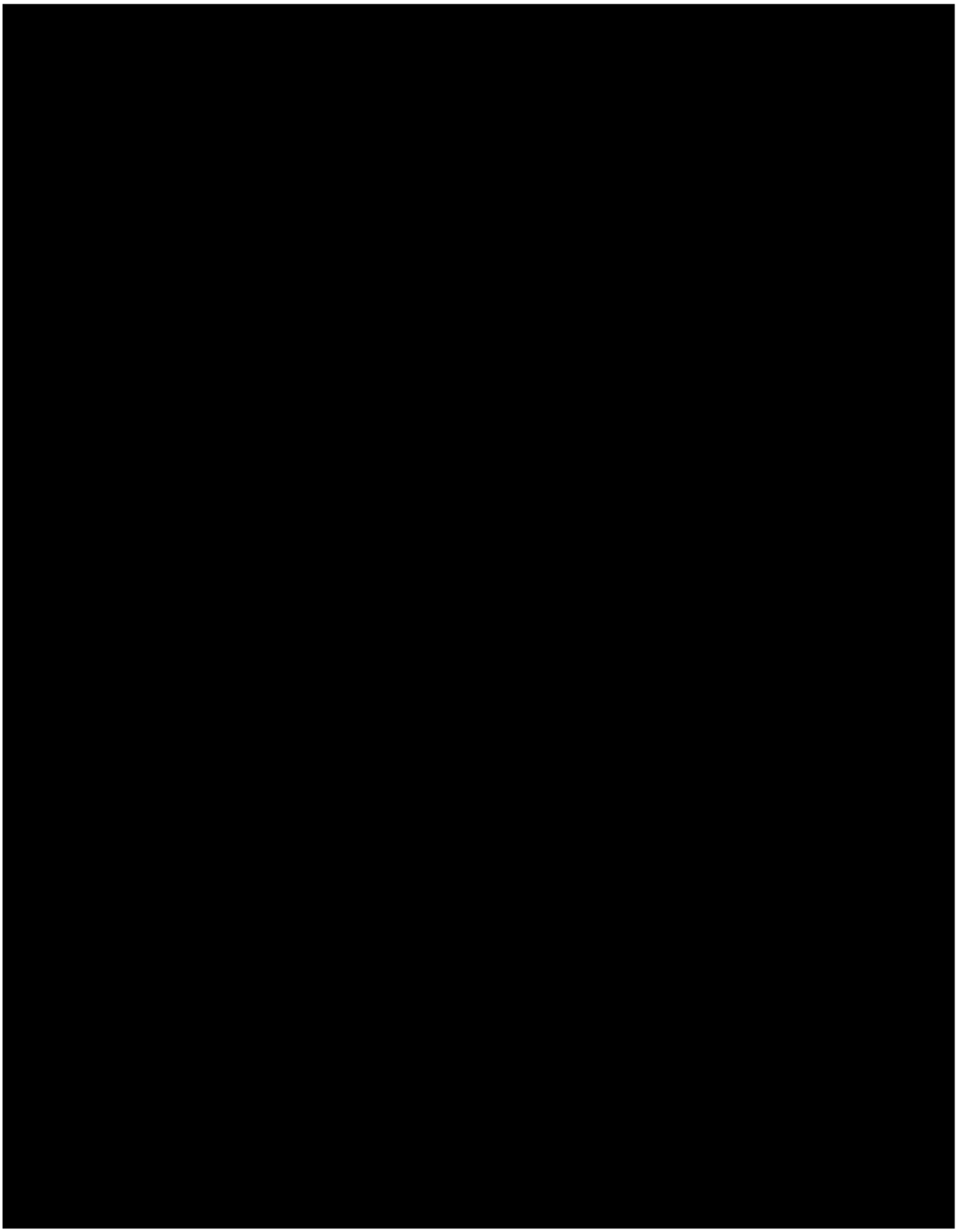
Do not write on the pouch label (foil pouch) with a pen, pencil, or marker directly.

At a minimum, each study drug label will provide the following information: product information, directions for use, and region-specific caution statements (including "New Drug – Limited by United States federal law to investigational use" language).

4.3.2 Directions for Administration and Removal

To apply and remove the study drug the following instructions should be provided to either study staff or subjects participating in the study.





4.4 Method of Randomization and Treatment Assignment

Each subject who is entered into the study will be assigned a screening number. The screening number will consist of the 2-digit site number (##) and a 3-digit sequential number (XXX). The subject screening number (##-XXX) becomes the subject identifier.

For subjects who meet the criteria for randomization, a treatment group randomization code will be assigned to that subject number via an Interactive Web Response System (IWRS). Subjects will then be centrally randomized in a 1:1 ratio to either SUN-131 1.5% TDS or placebo TDS. The randomization will be stratified by age group (<12 years, ≥12 years).

Re-screening of the same subject that has previously screen failed is allowed only once. Re-entry of the same subject that was previously randomized is allowed only once. A new subject number will be issued when the same subject is re-screened or re-enrolled for the study.

The study drug kit will be coded with a three-digit (YYY) kit number. After randomization on Day 1, the IWRS will assign a study drug kit to a subject. On Day 1, the subject will receive a 1-week supply of study drug including backup study drug. On Day 8 ± 1, the subject will visit the site, return all used and unused study drug, and be provided with another 1-week supply of study drug including backup study drug. On Day 15 ± 1, the subject will visit the site and return used and unused study drug.

4.4.1 Selection of Dose Used in the Study

All subjects assigned to the active treatment group will apply SUN-131 1.5% TDS to the study eyelid with a chalazion. This concentration and dose was selected based on the preliminary Phase 1 and Phase 2 studies conducted (SUN-131-01, SUN-131-02) that demonstrated excellent safety and comfort at this concentration. This is the maximum concentration tested in Phase 1 clinical trials.

4.4.2 Masking

Placebo TDS are manufactured to be the same patch weight and to be identical in appearance to the SUN-131 1.5% TDS, utilizing the same release liner, backing, and packaging components. Subjects will be assigned a study drug kit by the IWRS according to the randomization schedule. Investigators, subjects, and all study personnel (sites and sponsor) will be masked as to the identification of the active and placebo study drug.

Procedures will be in place for unmasking and are to be utilized only in the event of emergency or life-threatening condition where the medical management would be dictated by knowing the treatment status of the subject. The randomization code will be provided through the IWRS. The reason for treatment unmasking should be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must be

documented. The investigator should immediately contact the medical monitor via phone before unmasking a subject, unless it is not possible to do so without risk to the subject.

Subjects that are unmasked will be allowed to continue their participation in the study at the investigator's discretion, but the data may be excluded from the per-protocol analyses.

4.5 Prior Medication

On screening, site staff will review medication use to check for eligibility for the study. Use of medication listed below in the defined timeframe will exclude the subject from study participation.

- Use of systemic (intravenous, intramuscular, oral), ophthalmic, dermatological corticosteroids or immunosuppressant within 4 weeks prior to Day 1 and throughout the study period. Inhalant, intranasal, intra-articular, and perianal steroids are permitted.
- Use of systemic or ophthalmic azithromycin in either eye within 5 weeks prior to Day 1 and throughout the study period.
- Use of other systemic or ophthalmic macrolides (e.g. erythromycin, clarithromycin, etc.) in either eye within 2 weeks prior to Day 1 and throughout the study period.
- Use of tetracyclines (e.g. tetracyclines, doxycycline, etc.) in either eye within 2 weeks prior to Day 1 and throughout the study period.
- Use of periocular or intraocular corticosteroid injection or corticosteroid depot in either eye within 9 weeks prior to Day 1 and throughout the study period.

4.6 Concomitant Medications

Subjects will be allowed to use over-the-counter artificial tears or lubricant eye drops, over-the-counter anti-histamine drops administered by instillation into either eye, during the study as well as use of fluorescein sodium and benoxinate hydrochloride solution products (used when measuring IOP).

Use of periocular or intraocular (in either eye or eyelid), systemic (intravenous, intramuscular, oral), and dermatological corticosteroids during the study period will be prohibited. Inhalant, intranasal, intra-articular, and perianal steroids are permitted.

Use of systemic or ophthalmicmacrolides and tetracyclines in either eye will be prohibited during the study period.

Site staff will review ocular and non-ocular concomitant medication use at Visit 1 during subject screening. The use of any concurrent medication, prescription, or over-the-counter, will be recorded on the subject's source document and corresponding CRF along with the reason the medication will be taken.

4.7 Treatment Compliance

In this study, treatment will consist of wearing a total of 14 study drug for a minimum of 16 hours and maximum of 24 hours each day for 14 days. On Days 8 ± 1 and 15 ± 1, the study drug should not be replaced with a new study drug in the morning of the visit to ensure the study drug is worn for a minimum of 12 hours before removal by the investigator at the site. The subject may wear the study drug over 24 hours on these visit days if necessary. On Day 8 ± 1, subjects should apply a new study drug after completion of evaluations to ensure the study drug is worn for a minimum of 16 hours on that day. The subject can then return to their normal schedule of study drug removal and replacement. Subjects will record the time of application and time of removal of each study drug daily, any mis-application and fall-off as well as any unusual events in the electronic subject diary. Treatment compliance will also be assessed based on a subject diary, and all used and unused study drug returned at each visit. [redacted]

4.7.1 Study Drug Accountability

The Principal Investigator (PI) or designee is responsible for maintaining accurate records (including dates and quantities) of study drug received, subjects to whom study drug is dispensed (subject-by-subject dose specific accounting), and study drug lost or accidentally or deliberately destroyed. The PI or designee must retain all unused or expired study supplies until a Senju-designated Clinical Research Associate (CRA) has confirmed the accountability data.

4.7.2 Return and Disposition of Clinical Supplies

All used and unused study drug will be returned by the subjects and must be kept in a secure location for accountability and reconciliation by the Senju-designated CRA. The investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

Used study drug and unused study drug returned by the subjects are reconciled by the site against the study drug application and removal diary completed by the subjects. The Senju-designated CRA must account for all study drugs in a formal reconciliation process prior to return of study drug to the drug depot.

All study drug and related materials should be stored, inventoried, reconciled, and returned, according to applicable state and federal regulations and study procedures.

4.8 Dietary or Other Protocol Restrictions

No dietary restrictions will be imposed on study subjects.

Subjects will be asked not to take any other treatments for the chalazion or apply warm compresses to the study eyelid while in the SUN-131-03 trial. Subjects will also be asked to avoid wearing contact lenses and new facial cosmetic products during the study trial period. Subjects will be asked to avoid wearing any make-up, ointment, or moisturizer on the study eyelid with mascara on the eyelashes allowed during the study period.

5 EFFICACY AND SAFETY VARIABLES

5.1 Adverse Events (see Section 6)

For subjects who are experiencing ongoing unresolved and possibly related TEAEs at the time of study completion or early discontinuation from the study, it will be recommended that the investigator schedule an appropriate follow-up visit in order to determine the event outcome. If the outcome of the related TEAE cannot be determined during the follow-up visit, the investigator will make reasonable attempts to contact the subject via telephone, post, or certified mail for up to 30 days after study completion or early discontinuation from the study to assess the outcome of the event. Any additional data will be documented and made available to the sponsor. The sponsor medical monitor will determine when the data needs to be documented on the CRFs.

5.2 Ocular Safety Assessments

All ocular safety evaluations will be performed on both subject eyes at baseline (pre-dose on Day 1) and after the study drug removal on Days 8 ± 1 and 15 ± 1.

Intraocular pressure measurement (Goldmann applanation tonometry) should be done after the evaluations on chalazion and photography of chalazion and slit-lamp biomicroscopy evaluation are completed. All IOP pressure will be recorded in mmHg. To avoid IOP changes due to the diurnal rhythm, the IOP measurements should be performed at approximately the same time of the day on Days 1, 8 ± 1, and 15 ± 1. For subjects aged ≤ 12 years who have difficulty with Goldmann, Tono-Pen or iCARE may be used to measure IOP throughout the study. The same instrument should be used for measurement of the IOP for the study for each subject.

Visual acuity evaluation will be performed at all study visits with Snellen eye chart at 20 feet (6 meters). If the corrected or uncorrected VA is 20/40 or better, no additional refraction is necessary. If corrected or uncorrected VA is worse than 20/40, then an updated refraction must be performed. This refraction must be used for all VA assessments during the study. The subject must wear the same glasses, if applicable, at each visit. For subjects with surgical monovision correction, VA assessment may be conducted in the near vision eye with a near vision reading card held at approximately 14 inches from the subject's eye.

5.3 Skin Irritation Assessment (TDS Related Skin Irritation)

The investigator will assess skin irritation of the site application area for the TDS separate from the area affected by the study chalazion (i.e., excluding the chalazion itself) on the study eyelid. This skin assessment of the surrounding area will be conducted at baseline (pre-dose on Day 1) and after the study drug removal on Days 8 ± 1 and 15 ± 1. On Days 8 ± 1 and 15 ± 1, assessments will be conducted approximately 30 minutes to 1 hour after study drug removal in the clinic. This evaluation should be done by the same investigator throughout the study period as much as possible.

Table 2: Dermal Response Scale (Draize)

Score	Score Description
0	No evidence of erythema
1	Very slight erythema
2	Well defined erythema
3	Moderate to severe erythema
4	Severe erythema (beet redness) to slight eschar formation (injuries in depth)

5.4 Patch Adhesion Evaluation

The patch adhesion will be evaluated by the investigator using the following 5-point scale prior to patch removal on Days 8 ± 1 and 15 ± 1 in the study eyelid only. This evaluation should be done by the same investigator throughout the study period as much as possible.

0 = ≥90% adhered (essentially no lift off of the skin)
1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin)
2 = ≥ 50% to < 75% adhered (less than half the system lifting off the skin)
3 = < 50% adhered (more than half the system lifting off the skin without falling off)
4 = patch detached (patch completely off the skin)

5.5 Ocular and Skin Comfort Query

Subjects will be asked to assess the ocular and skin comfort query of the eye of the study eyelid and study eyelid prior to application of the first study drug at baseline (Day 1) and prior to patch removal on Days 8 ± 1 and 15 ± 1 using a subjective 100 mm Visual Analog Scale (VAS) where 0 mm = very comfortable and 100 mm = very uncomfortable. There will be no descriptors for numbers other than 0 mm and 100 mm on the scale and meaning of the extreme ends of the scale. VAS scores will be collected electronically as part of the subject electronic diary.

5.6 Presence of a Chalazion

The presence or complete absence of a chalazion on the study eyelid will be evaluated by the investigator at each study visit at screening/baseline (Day 1), and at 30 minutes to 1 hour after patch removal on Days 8 ± 1 and 15 ± 1. Absence of a chalazion is determined by the investigator's clinical judgment and may accompany scarring or skin defects resulting from healing of the chalazion. This evaluation should be done by the same investigator throughout the study period as much as possible.

Subjects will also document in their subject electronic diary if the chalazion is still present or not daily from Day 1 through Day 15 ± 1.

5.7 Size of the Chalazion

The size of the chalazion on the study eyelid will be evaluated by the investigator at each study visit at screening/baseline (Day 1), and at 30 minutes to 1 hour after patch removal on Days 8 ± 1 and 15 ± 1. The size will be measured [redacted] The size will not be evaluated on Days 8 ± 1 and 15 ± 1 if the study chalazion is determined to be absent. This evaluation should be done by the same investigator throughout the study period as much as possible.

5.8 Erythema of the Chalazion

The investigator will assess erythema of the chalazion on the study eyelid at each study visit at screening/baseline (Day 1), and at 30 minutes to 1 hour after patch removal on Days 8 ± 1 and 15 ± 1. The quantitative scale for this assessment is described below (Table 3). This evaluation should be done by the same investigator throughout the study period as much as possible.

Table 3: Erythema of the Study Chalazion

Score	Score Description
0	No signs of erythema
1	Slight erythema
2	Mild erythema
3	Moderate erythema
4	Severe erythema

5.9 Pain Associated with Chalazion Assessment

Subjects will be asked to assess the pain associated with the chalazion using a VAS. The VAS will be specific for pain associated with the chalazion by asking the following questions: "How intense is your pain associated with the chalazion in your eyelid" and "How intense is your pain associated with the chalazion in your eye". For each question, a 100 mm VAS will be used with no numbers or hash marks. This assessment will be done at screening/baseline (Day 1), and at 30 minutes to 1 hour after patch removal on Days 8 ± 1 and 15 ± 1. The pain will not be evaluated if the study chalazion is determined to be absent. The VAS scores will be collected electronically as part of the subject electronic diary.

5.10 Appropriateness of Measurements

The ocular safety measurements used in the study (AEs, VA, slit-lamp biomicroscopy, IOP measurement) are generally recognized as reliable, accurate, and relevant in assessing the safety of topical ophthalmic pharmaceutical drugs.

This is the first study to evaluate a transdermal delivery methodology for ophthalmic medication; it is thus considered appropriate to capture the subject's impressions of ocular and dermal comfort during and after wearing the study drug. For both assessments, the subjects will use a 100 mm VAS, where 0 mm = very comfortable and 100 mm = very uncomfortable, to rate the comfort.

The Draize scale that will be used for scoring dermal response (see Table 2) caused by the study drug, as well as the scale that will be used to evaluate patch adhesion (see Section 5.4), have been widely used by all regulatory authorities for evaluation of skin irritation (4).

The primary endpoints are clinical evaluation of the eyelid and determination of the presence or absence of a chalazion. While slight scarring or distortion of the skin may remain due to the granuloma, the assessment of healing of the chalazion will be based on clinical judgment. Subjects who exhibit a complete resolution of the chalazion based on clinical examination at any time in the study will be considered a CR.

The secondary outcome measures include time to CR of the chalazion as documented by the subject in the patient diary. The size of the study chalazion will also be evaluated and its rationale given that complete resolution may not occur; however, the size of the chalazion may be significantly reduced with treatment. The erythema of the chalazion site itself will also be assessed using a 5-point scale common in ophthalmology for evaluating the redness of the chalazion. In some cases, the chalazion can cause pain either in the eyelid or the eye itself. As such, a pain VAS will be used to ask the subject to assess either the pain in the eyelid caused by the chalazion or the pain in the eye itself that may occur due to pressure on the eye from the chalazion.

5.11 Primary Efficacy Variables

The primary efficacy variables in this trial are the CR of the study chalazion by Day 15 ± 1. Complete response is defined as the absence of any significant clinical signs of a chalazion, based on clinical judgment by an investigator. Scarring or skin defects resulting from healing of the chalazion are possible and allowed upon CR.

5.12 Secondary Efficacy Variables

[redacted]

5.13 Drug Plasma Concentration Measurements

No pharmacokinetic sampling will be taken in this protocol.

6 ADVERSE EVENTS

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study drug or other protocol-imposed intervention, regardless of attribution. An AE may include intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions (e.g., worsening of asthma).

The reporting period for AEs (non-serious and serious) starts after the first study drug application on Day 1 and ends at Follow-Up Telephone Contact (Day 22 ± 3).

The investigator will assess AEs for severity, for relationship to investigational product (IP), and as to whether the event meets one or more of the definitions of a serious adverse event (SAE) (see Section 6.1).

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0. The investigator will determine the severity of each AE based on NCI CTCAE criteria and will record the grade of the event on the source documents and AE CRF.

NCI CTCAE Grade	Common Term	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-Threatening	Life-threatening consequences; urgent intervention indicated.
5	Death	Outcome of AE was death.

***Please note**: severity of an event does not necessarily correlate to the event being defined as a Serious Adverse Event (SAE).

The investigator will determine the relationship of an AE to the IP and will record it on the source documents and AE CRF, using the categories defined below.

Causality Category	Description
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. For the purpose of this protocol, the term unlikely will be considered not related to study medication and an "Adverse Event".
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. For the purpose of this protocol an event that has possible relationship to study medication will be defined as a "Suspected Adverse Drug Reaction".
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal. For the purpose of this protocol an event that has probable relationship to study medication will be defined as an "Adverse Drug Reaction".

In order to classify AEs and diseases, preferred terms will be assigned by the sponsor or its designee to the original terms entered on the CRF, using MedDRA (version 19.1).

An Unexpected AE is defined as an adverse reaction, the nature or severity of which is not consistent with the product information provided in the Investigator's Brochure.

The medical monitor, in consultation with the investigator, will be responsible for determining without unmasking the subject, whether an AE is clinically significant for the subject or the study overall.

Should a pregnancy occur, it must be reported and recorded on the pregnancy form. Treatment should be stopped at the time when the pregnancy is reported. Pregnancy in itself is not regarded as an AE. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

6.1 Serious Adverse Events

An SAE is defined as any AE that:

- Results in death (i.e., the AE actually causes or leads to death);
- Is life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death);
- Requires or prolongs in-patient hospitalization;
- Results in persistent or significant disability or incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions);
- Results in a congenital anomaly or birth defect in a neonate/infant born to a mother exposed to IP prior to conception or during pregnancy;
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or require medical or surgical intervention to prevent 1 of the outcomes listed above).

The reporting period for SAEs will begin after the first study drug application on Day 1 and continue through Day 22 ± 3. Serious AEs reported to the investigator outside of this reporting period will be reported to Senju or the medical monitor, if, in the investigator's judgment, the event has any bearing on the study data. SAEs must be followed by the investigator until resolution, or until the subject is lost to follow-up, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

Any SAE, whether or not considered a suspected adverse drug reaction, will be reported immediately (within 24 hours of learning of the event) by fax or email using the study-specific SAE Report Form. In addition to the outcome of the SAE, any medication or other therapeutic measures used to treat the event will be recorded on the appropriate CRF page(s). Investigators should not wait to collect additional information that fully documents the event before notifying Senju of an SAE. Senju may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that Investigators submit additional information requested by Senju as soon as it becomes available.

Reporting of SAEs to the IRB/EC will be done in compliance with the standard operating procedures and policies of the IRB/EC and with applicable regulatory requirements. Adequate documentation must be obtained by Senju showing that the IRB/EC is properly and promptly notified as required.

The SAE form must be either faxed to +1-877-464-7787 or emailed within 24 hours to INCDrugSafety@incresearch.com.

The investigator is encouraged to discuss with the medical monitor any AEs for which the issue of seriousness is unclear or questioned. Contact information for the medical monitor is as follows:

Medical Monitor: [redacted]
Cellular: [redacted]
Email: [redacted]

7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

All data collected on CRFs will be presented in data listings. The primary and secondary endpoints for this trial will be evaluated using the Intent-to-Treat (ITT) population with the Modified Intent-to-Treat (mITT) performed as a sensitivity analysis. The safety analyses will be carried out using the safety population. Comfort scores (ocular, skin, and the average of both), patch adhesion, and residual drug content will be analyzed using the ITT population (and mITT and Per-Protocol [PP] populations if there are subjects with protocol deviations or incomplete data). In general, the grade for each measure in each eye will be used for analysis of treatment effects unless otherwise specified. All analyses will be conducted in a validated instance of SAS 9.1 or higher.

7.1.1 Analytical Populations

- **Intent-to-Treat**: The ITT population will include all randomized subjects. All primary and secondary efficacy analyses are to be on the ITT population.
- **Modified Intent-to-Treat**: The mITT population will include all randomized subjects with at least one post-baseline primary outcome assessment. Results of the efficacy analyses based on the mITT population will be presented as a sensitivity analysis. Treatment assignments in the mITT population will be based on the treatment to which the subject was randomized.
- **Safety**: The safety population will include all randomized subjects who received the study drug. Treatment assignments in the safety population will be based on the treatment that was received (if different from the randomized treatment).
- **Per-Protocol**: The PP population will exclude from mITT population those subjects who have major protocol violations. Major protocol violations include violation of entry criteria, receiving the incorrect randomization, noncompliance with study drug administration (missing the study drug administration more than 80% of study drug or failure to apply the study drug for at least 5 days per week and miss more than 2 of 7 days of application), and the use of prohibited medications. Treatment assignments in the PP population will be based on the treatment that was received (if different from the randomized treatment).

7.1.2 Analysis of Subject Disposition

Disposition will be summarized for subjects enrolled into the study. For the subjects who are enrolled, summaries will be presented for the number and percentage of subjects who completed the study and for those who prematurely withdrew. The reason for withdrawal will be summarized by number and percent for subjects who prematurely withdrew. Visit attendance will be summarized for all enrolled subjects.

A list of subjects with protocol violations and their specific violations will also be provided. A separate listing will indicate all mis-assignments or out of sequence assignments of study drug according to the randomization code list and the reason for the error.

7.1.3 Analysis of Demographic and Background Characteristics

The demographic data will be summarized for the ITT population. Demographic data (age, gender, ethnicity, race, iris color, chalazion onset, chalazion erythema score at baseline) will be presented for each group (SUN-131 1.5% TDS and placebo TDS), and for all enrolled subjects combined. Baseline medical history will be summarized and a subject listing will be provided. A summary of all prior and concomitant medications will be presented in tabular form by therapeutic drug class and generic drug name using the World Health Organization (WHO) Drug classification. A summary of all prior and concomitant therapy will be summarized. Ocular and non-ocular medical histories will be presented in Appendices.

7.1.4 Analysis of Study Medication Compliance and Exposure

Study medication compliance entails wearing the study drug for minimum of 16 hours and maximum of 24 hours each day for 14 days. Compliance will be assessed through Visit 3 by patch adhesion assessments carried out by the investigator, by subject diaries and by collection of all used and unused study drug. The patch adhesion scores and their changes from baseline will be summarized by treatment group using descriptive statistics (number of subjects, mean, median, range, and standard deviation). Exposure of the study will be summarized by treatment group using descriptive statistics (number of subjects, number of study drug applied, number of days applied, number of hours applied, mean, median, and standard deviation).

7.1.5 Analysis of Efficacy

7.1.5.1 Primary Efficacy Analysis

The primary analysis will compare the proportions of subjects in the 2 groups who experience CR of the study chalazion on or before Day 15 ± 1. CR is defined as the absence of any significant clinical signs of a chalazion with possible scaring or skin defects resulting from healing of the chalazion allowed. The primary analysis will be conducted using Pearson's chi-square test (two-sided) at the alpha = 0.05 level of significance.

7.1.5.2 Key Secondary Analyses

7.1.5.3 Other Efficacy Analyses

All quantitative secondary endpoints will be analyzed using the two-sample t-test (parametric) and the Wilcoxon-Mann-Whitney test (nonparametric). Secondary endpoints that are defined as time-to-event variables will be summarized using the Kaplan-Meier method; the log-rank test will be used to compare the distributions in the 2 groups. The primary and secondary endpoints will also be analyzed in the PP population. All secondary analyses will be conducted using two-sided tests at the alpha = 0.05 level of significance.

7.1.6 Analysis of Safety and Other Measures

Safety measures include AEs, ocular examinations and assessments (VA, slit-lamp biomicroscopy, IOP measurement), and skin irritation assessments.

The number and percentage of subjects reporting AEs during the study will be tabulated by MedDRA SOC and by preferred term within each organ. The AE tables will be separately presented by ocular and non-ocular. Ocular AEs will be tabulated by maximum severity and maximum relationship to treatment. For non-ocular AEs, tables will be generated in the same fashion of ocular AE tables, if necessary. System organ classes summary will be listed with eye disorders first, followed by SOCs listed in order of descending frequency for all subjects. Preferred terms will be listed in order of descending frequency within each SOC. Summaries and listings will be provided for subjects reporting SAEs, subjects experiencing AEs related to study medication, and subjects withdrawing due to an AE. The percentages of specific AEs between treatments may be analyzed using Fisher's exact test if they are extremely unbalanced between groups.

Slit-lamp biomicroscopy will be performed at baseline (pre-dose on Day 1) and just after patch removal on Days 8 ± 1 and 15 ± 1. All biomicroscopy findings will be graded Normal, Abnormal (not clinically significant), or Abnormal (clinically significant) by the investigator. The frequency distribution (number and percentage) of findings in each treatment group at baseline will be tabulated along with the frequency distribution at each time point. The percentages of slit-lamp biomicroscopy findings between treatments may be analyzed by using Pearson's chi-Square test or Fisher's exact test, if necessary, at each time point.

Visual acuity, IOP, ocular comfort score, skin comfort score, and the patch adhesion assessment score will be summarized using descriptive statistics (number of subjects, mean, median, range, and standard deviation) at each time point. The SUN-131 1.5% TDS will be compared to the placebo TDS results at each time point. The changes from baseline (Day 1) will be calculated and the groups compared. A paired t-test will be used to compare the treatment groups at each time point. Additionally, a Wilcoxon signed-rank test may be used for analysis of the skin irritation scores if the distribution of data appeared to be not normally distributed. All statistical testing will be evaluated using a level of significance (α) of 0.05.

7.1.7 Determination of Sample Size

7.1.8 Methods for Handling Missing Data

The primary endpoint is defined as CR by Day 15 ± 1. For this endpoint, if a subject has missing data at the specified time point, but is known to be a complete responder at an earlier assessment, the subject will be defined as having CR. However, a subject whose prior status is unknown will be defined to be a non-responder. Subjects with missing data at Day 8 and Day 15 will be considered non-responders. Subjects with missing data at Day 8 but with data at Day 15 will be assigned as a responder or non-responder based on their Day 15 results. Subjects who are responders on Day 8 will be considered responders for the purposes of the trial regardless of the Day 15 evaluation.

For all time-to-event endpoints, subjects who do not achieve the endpoint will be censored at the date of their last assessment.

For quantitative secondary endpoints, missing data will not be imputed.

8 ETHICS

8.1 Institutional Review Board or Ethics Committee

Prior to initiating the study, the investigator will obtain written confirmation that the IRB or EC is properly constituted and compliant with all US FDA requirements and local regulations. A copy of the confirmation from the IRB/EC will be provided to Senju or its designee. The PI will

provide the IRB/EC with all appropriate material, including the protocol, IB, the ICF, and any other written information provided to the subjects, including all consent forms translated to a language other than the native language of the clinical site. The study will not be initiated until appropriate IRB/EC approval of the protocol, the ICF, and all subject recruitment materials are obtained in writing by the PI and copies are received at Senju or its designee. The approval document should refer to the study by protocol title and Senju, protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. Appropriate reports on the progress of the study will be provided to the IRB/EC or Research Ethics Board (REB) and Senju or its designee by the PI in accordance with applicable governmental regulations and in agreement with policy established by Senju.

8.2 Ethical Conduct of Study

This study will be conducted in accordance with the Declaration of Helsinki and GCP according to ICH guidelines. Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an IRB/EC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject, or his/her legally authorized representative will provide written, informed consent before any study-related tests or evaluations are performed.

8.3 Subject Information and Informed Consent

A properly written and executed ICF, in compliance with the Declaration of Helsinki, ICH GCP and US Code of Federal Regulations (CFR) for Protection of Human Subjects (21 Code Federal Regulation CFR50.25, CFR50.27, and CFR Part 56, Subpart A), and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The investigator will prepare the ICF and provide the document to Senju or its designee for approval prior to submission to the IRB/EC. Senju and the IRB/EC must approve the document before it is implemented. If a subject is unable to sign the ICF, a legal representative may sign for the subject. The investigator will provide copies of the signed ICF to each subject (or the subject's legal representative) and will maintain the original in the subject's record file.

9 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prior to beginning the study, the PI at each site must provide to Senju or its designee a fully executed and signed Form FDA 1572. All sub-Investigators must be listed on Form FDA 1572.

The study will be administered and monitored by employees or representatives of Senju. CRAs will monitor site on a periodic basis and perform verification of source documentation for each subject as well as other required review processes. Senju's designee will be responsible for the timely reporting of SAEs to appropriate regulatory authorities as required.

10 ELECTRONIC CASE REPORT FORMS AND SOURCE DOCUMENTS

Electronic case report forms will be provided for each subject. The investigator must review and sign the completed eCRFs to verify their accuracy.

Unless explicitly allowed in the eCRF instructions, blank data fields are not acceptable. If corrections are made after review and approval by the investigator, he or she must confirm and endorse the changes. The study staff will be queried for clarification regarding incomplete entries.

Senju's policy is that study data on the eCRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subject records. In addition, all source data should be attributable (signed and dated). The investigator must therefore agree to allow direct access to all source data. Subjects (or their legal representatives) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent. If an investigator or institution refuses to allow access to subject records because of confidentiality, arrangements must be made to allow an "interview" style of data verification.

A CRA designated by Senju will compare the eCRFs with the original source documents at the study site and evaluate the eCRFs for completeness and accuracy. If necessary, the study site personnel will be contacted for corrections and/or clarifications. The investigator or designee must also review and sign all electronic Data Clarification Forms (eDCFs) or the corrections to the eCRFs to verify their accuracy prior to submission to Senju or its designee. Data that are modified via eDCFs must be supported in the source documents.

Designated site personnel must complete eCRFs as soon as possible after a subject visit, and the forms must be available for review at the next scheduled monitoring visit.

11 STUDY MONITORING AND AUDITING

Qualified individuals designated by Senju will monitor all aspects of the study according to GCP and standard operating procedures for compliance with applicable government regulations. The PI agrees to allow these Senju-designated CRAs direct access to the clinical supplies, dispensing, and storage areas and to the clinical files, including original medical records of the study subjects. The PI and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by Senju or its designees.

Members of Senju GCP Compliance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The PI will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other regulatory agencies may also conduct an audit of the study. If informed of such an inspection, the

PI should notify Senju immediately. The PI will ensure that the auditors have access to the clinical supplies, study site facilities, original source documentation, and all study files.

12 RETENTION OF RECORDS

The PI must retain all study records required by Senju and by the applicable regulations in a secure and safe facility. The PI must notify Senju of any change in the location, disposition, or custody of the study files. The PI/institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or contemplated marketing applications in the US or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. No records relating to this study should be disposed of without the written approval of Senju. It is the responsibility of Senju to inform the PI/institution as to when these documents no longer need to be retained.

13 DISCLOSURE OF DATA

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the US FDA, national and local health authorities, Senju and the IRB for each study site, if appropriate.

14 REFERENCES

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4. Draize JH. Dermal toxicity. Appraisal of Chemicals in Food, Drugs and Cosmetics: The Association of Food and Drug Officials of the United States (3rd printing 1975); 1959. p. 46-59.