Clinical Trial to Evaluate ET-01 in Subjects with Lateral Canthal Lines

Protocol No.: ET-01-LCL-208

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ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis Of Variance
BoNTA	Botulinum toxin, Type A
CFW	Crow’s Feet Wrinkle (scale)
eCRF	Case Report Form
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment score
IGA-C	Investigator's Global Assessment score on Contraction
IGA-R	Investigator's Global Assessment score at Rest
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intra-Uterine Device
LCL	Lateral Canthal Lines
LOCF	Last Observation Carried Forward
PP	Per-Protocol
SAE	Serious Adverse Event
SSA	Subject Self-Assessment
SSA-C	Subject Self-Assessment on Contraction
SSA-R	Subject Self-Assessment at Rest

1 INTRODUCTION AND BACKGROUND

Over time, the actions of the facial musculature, coupled with loss of skin elasticity and a reduction in subcutaneous tissue, result in the development of facial lines. With the decrease in skin elasticity, repeated facial expressions can become permanent lines[1]. The periorbital area is one of the first places on the face to show signs of aging, in the form of lateral canthal lines or Crow's Feet. Genetic differences and environmental toxins, predominantly ultraviolet light exposure and cigarette smoking, may alter the rate of this normal aging process[2].

Over the past two decades, there has been increasing demand for aesthetic procedures to reverse the effects of aging, particularly in the facial area, and treatment of Crow's Feet is among the most frequent of corrective treatment requests. A number of techniques have been developed to meet the increasing demand for aesthetic procedures to reverse the signs of aging. These include: incisional and excisional surgery, various resurfacing procedures, and the use of temporary or semi-permanent, injectable dermal fillers such as allogeneic or xenogeneic collagen, hyaluronic acid, and autologous fat cells. Topical agents, such as retinoic acids, glycolic acids and lactic acids, are other common methods to minimize Crow's Feet and other facial wrinkles.

Injection of *botulinum* toxin type A (BoNTA) is now one of the most common aesthetic procedures performed and there is a considerable body of medical literature demonstrating its safety and efficacy in aesthetic indications[3]. On a molecular level, *botulinum* toxin prevents the release of preformed mediators, such as acetylcholine, from motor nerve endings leading to a flaccid paralysis.

BoNTA is an effective treatment for Crow's Feet and is associated with high subject satisfaction. However, the treatment requires multiple injections into a well innervated, sensitive area that is prone to bleeding and bruising and close to delicate organs such as the eyes and lachrymal glands. In addition, misplacement of injection can lead to unwanted effects in non-target areas. Therefore, a topical dermatological formulation to deliver the active ingredient, avoiding the discomforts and potential side effects of injections, would be highly desirable.

Several studies have been conducted assessing the dose-response of the topical *botulinum* product, ET-01[4], in the treatment of Crow's Feet. The product was well tolerated. This current clinical trial seeks to expand on the existing work.

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[1] Ascher, B et al. Dermatol Surg 35:1478-1486, 2009

[2] Carruthers, A et. al. Dermatol Surg 2008; 34:S173–S178

[3] Coté, T. et al. J. Am. Acad. Dermatol. 2005;53:407-15

[4] ET-01 was previously studied under Anterios' code ANT-1207 and ANT-1401

2 STUDY OBJECTIVES AND PURPOSE

In a previous study ET-01 was applied at doses of up to 1,150 U after skin pre-conditioning with microneedle arrays of the type AdminStamp. The purpose of this Phase 2 study is to repeat the prior study using a different device for skin pre-conditioning, i.e. a Dermaroller.

3 STUDY DESIGN

3.1 Overall Design

The study will be an out-patient, prospectively randomized, double-blind, vehicle-controlled, two-armed, overlapping, sequential ascending dose group, multi-center clinical trial. Each cohort will be fully enrolled and complete the Week 4 visit to allow for a safety review before initiating enrollment of the next dose group.

3.2 Treatment Groups / Sample Size

The following dose groups and sample sizes are planned:

Dose Group		Vehicle	690 U	1,100 U	∑ Total
Cohort 1	N =	12	24		
Cohort 2	N =	12		24	
Total	N=	24	24	24	72

The treatment area will be preconditioned with a Dermaroller MC 905, 0.5 mm. ET-01 will be applied immediately after pre-conditioning.

3.3 Efficacy Parameters and Timing

Efficacy will be assessed using the Crow's Feet Wrinkle Scale (CFW), which is a published validated, photo-numeric guide that grades severity of lateral canthal lines into one of the five categories of 0=none, 1=minimal, 2=mild, 3=moderate, and 4=severe. (see Appendix A for details). Using the same scale, assessments will be made by both, the investigator (IGA) and the subjects (SSA). Assessments are made "static" to avoid recall bias.

The IGA and SSA are recorded separately for the right and left canthal areas, both "at rest" and "on contraction". The IGA and SSA will be recorded at each visit.

3.4 Safety Parameters and Timing

Safety will be assessed during the study by collection of study events, review of concomitant treatments and laboratory data. Clinical adverse event reporting will be conducted at each visit.

All laboratory measurements will be performed by a central laboratory using appropriate and validated methods. Values will be reported to the Investigator and the Sponsor. Laboratory reference range values will be described in the laboratory manual. Investigators will assess all out of range values as being clinically significant or not.

3.4.1 Vital signs

Weight, height (Screening visit only) temperature, resting pulse, blood pressure, and respiration rate. Vital signs will be recorded at every visit.

3.4.2 Muscle Weakness or Paralysis

Participants will be monitored for potential signs of *botulinum* induced muscle weakness or paralysis. Subjects will be evaluated for Signs of Botulinum Toxin Spread (muscle weakness - ocular and the extremities) or difficulty swallowing or breathing (cranial nerve assessment, Appendix B).

The neurologic assessments are made at Baseline, Week 1, 2, and Week 4.

3.4.3 Hematology

Non-fasting clinical hematology evaluations are:
hemoglobin, hematocrit, red blood cell count, white blood cell count, with a differential, and a platelet count.

Non-fasting clinical hematology evaluations will be performed at Week 0 (Baseline), Week 4, and Week 26/End of Study.

3.4.4 Clinical Chemistry

A standard non-fasting chemistry panel will be performed which will include the following parameters:
glucose, uric acid, calcium, sodium, potassium, phosphorus, chloride, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, bicarbonate, creatinine, blood urea nitrogen, lactate dehydrogenase, total protein, albumin.

The chemistry panel will be performed at Baseline (Week 0), Week 4, and Week 26/End of Study. A urine pregnancy test will be performed for women of child-bearing potential at Baseline and the Week 4 visit.

3.4.5 ECG Testing

A 12-lead ECG will be recorded measuring the RR, PR, QRS, and QT interval durations prior to treatment application at Baseline and at Week 2.

3.4.6 Immunogenicity

Plasma samples will be banked for future analysis of anti-botulinum serum antibodies as a safety parameter for possible immunization against botulinum.

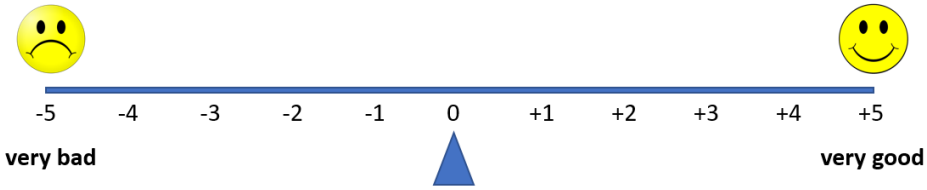
Samples will be taken at Baseline, Week 4, and Week 26.

3.4.7 Photography

Color photographs will be taken at every visit. Five pictures will be taken as described in Appendix C.

3.4.8 Treatment Procedure

To capture the level of comfort or discomfort caused by the skin pre-treatment with the Dermarollers and subsequent rubbing in of the study medication subjects will be asked to rate their experience on a scale from “-5” (very bad) to “+5” (very good).



3.5 Study Visits and Procedures

A schematic study diagram is shown below:

Procedure	Scr./BL	W 1	W 2	W 4	W 8	W 12	W 18	W 26	
	Day 0 ± 0	Day 7 ± 2	Day 14 ± 3	Day 28 ± 4	Day 56 ± 7	Day 84 ± 7	Day 126 ± 7	Day 182 ± 7	End of Study[#]
Informed Consent	X								
Assess Eligibility & Medical History	X								
Review Con-meds	X	X	X	X	X	X	X	X	
Record AEs	X	X	X	X	X	X	X	X	
Weight and Vital Signs	X	X	X	X	X	X	X	X	
Signs of Botulinum Spread	X	X	X	X					
Hematology and Chemistry	X			X					X
Anti-Botulinum Antibodies	X			X					X
Urine Pregnancy test (WOCBP)	X			X					
ECG	X		X						
IGA Score	X	X	X	X	X	X	X	X	
Subject Self-Assessment (SSA)	X	X	X	X	X	X	X	X	
Photography	X	X	X	X	X	X	X	X	
Randomization	X								
Apply Study Medication	X								

[#] also for early termination

The study will consist of up to 8 office visits.

3.6 Measures to Minimize/Avoid Bias

To minimize bias, subjects will be randomly allocated to one of the three treatment groups, i.e. vehicle (group A) vs. low dose (group B) vs. high dose (group C). Neither subjects nor investigators will be aware of the treatment allocation.

4 MEDICATION AND DOSING

4.1 Dose Rationale

Finding evidence of a safe and effective dose is the purpose of this study. In previous clinical studies doses of up to 2,000 U were applied under occlusion and were well tolerated. In study LCL-206 which employed microneedle skin preconditioning, doses of up to 1,150 U were applied safely. In this study, a different microneedle device is used for skin pre-conditioning. In case this may lead to somewhat better relative bio-availability, this study, LCL-208, will start at 690 U or 5/8 of the maximum dose administered in study LCL-206. After a safety review, it is planned to dose escalate by factor 1.6 to 1,100 U, a level just below the maximum dose level of study LCL-206.

4.2 Treatment of Subjects

The study preparation or vehicle consists of a milky, white lotion of low viscosity. The drug product and diluents will be provided in kits containing 3 mL dropper bottles that contain either ET-01 or Vehicle.

The following dose groups and sample sizes are planned:

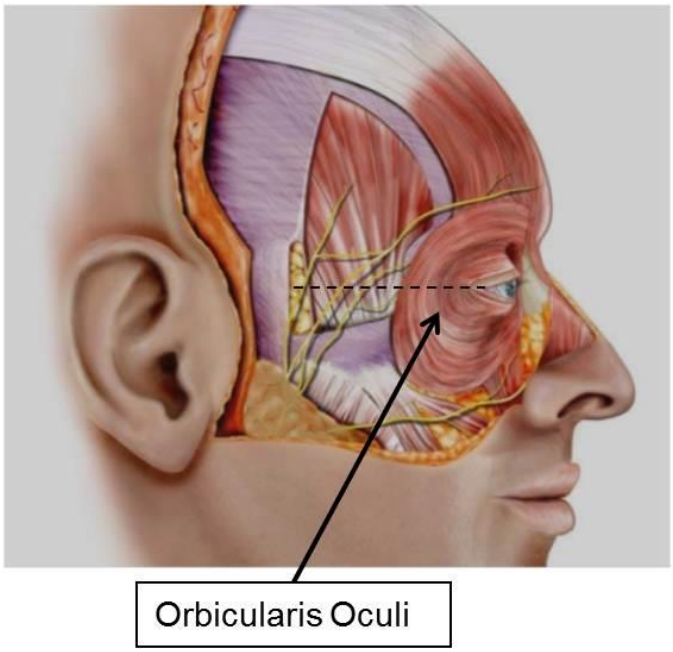
Dose Group		Vehicle	690 U	1,100 U	∑ Total
Cohort 1	N =	12	24		
Cohort 2	N =	12		24	
Total	N=	24	24	24	72

Randomization to a treatment group, i.e. ET-01 or Vehicle, will be obtained following a randomization list prepared by the Sponsor. Allocation to a dose level will be driven by sequence of enrollment.

The study medication will be applied TOPICALLY and only to subject's canthal areas. The site will be instructed to make sure no syringes or needles are present in the treatment room before study medication is brought into the room.

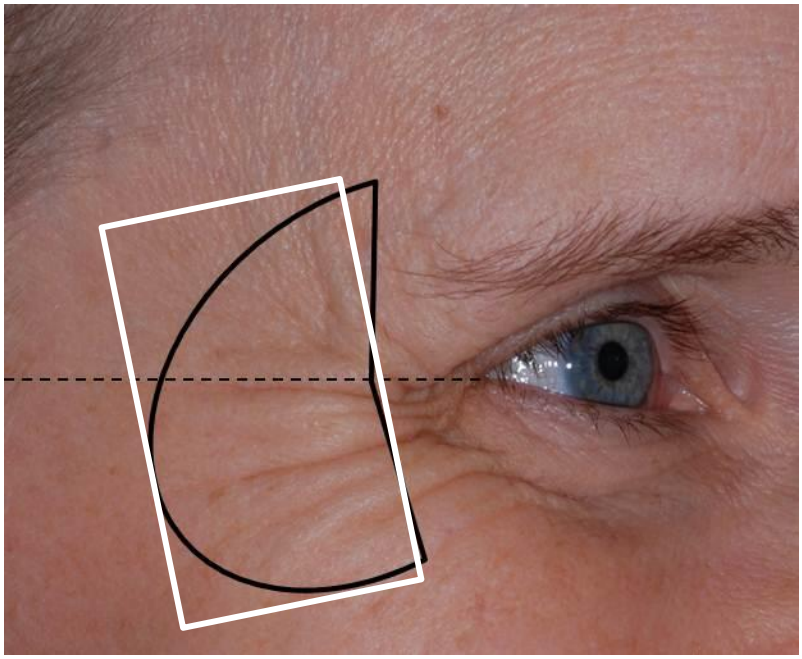
The treatment area is the periorbital region in the distribution of the muscles responsible for the Crow's Feet wrinkles. The muscle being treated to reduce the Crow's Feet wrinkle – the *orbicularis oculi* – is illustrated Figure 1.

Figure 1: *M. orbicularis oculi*



In general, the treatment region begins on the bony rim of the orbit, extending laterally to approximately one centimeter from the exterior edge of the hairline, 1 - 1.5 cm above and 1.5 – 2 cm below a horizontal line emanating from the lateral canthus to the hairline. This area of application is illustrated by the black outline in the picture below:

Figure 2: Treatment Area



As a guide to treatment, it is helpful to have the subject contract the orbicularis oculi muscle by asking the subject to produce a maximal smile so that the muscular extension can be visualized for that subject's treatment. In no case, however, should ET-01 ever be applied within the area circumscribed by the interior edge of the orbital rim.

The clinical investigator will wipe the periorbital region with an alcohol wipe and then dry thoroughly with a cotton swab. The treatment area will be pre-conditioned by pressing the Dermaroller firmly, applying approximately 2-3 pounds of pressure, to the skin. The location of the area of pre-conditioning are illustrated by the white outline in Figure 2. There will be ten (10) rolls made along the bony rim of the orbital cavity in an up-and-down motion. After each roll of the Dermaroller, the Dermaroller will be lifted off the skin. The first roll will start at the area of the skin corresponding to the superior aspect of the outlined white box and then rolled downward. The second roll will start at the area of the skin corresponding to the inferior aspect of the outlined white box - slightly offset from the first roll - and then rolled upward. Thereafter, each roll will start at the area of the skin corresponding to the superior aspect of the outlined white box, followed by a roll that will start at the area of the skin corresponding to the inferior aspect of the outlined white box.

Immediately thereafter, using a gloved finger, the investigator will massage 8 drops of the topical treatment into the skin of the treatment area.

The medication is of low viscosity and administered one drop at a time to avoid run-off. As an additional precaution, the subject will be positioned on an examination table or fully reclined examination chair such that his/her temple will slightly slant backwards and to the side, directing any run-off away from the eyes and into the hairline. The subject will be instructed to close his/her eyes which will then be covered with eye covers, e.g., IPL-Aid™ Disposable Eye Shields, and an absorbent paper or cloth.

There are 3 phases that the study drug will go through before it is completely absorbed into the skin. The clinical investigator will be instructed to make sure to visually observe all 3 phases during application process before additional small aliquots of Test Article are applied as listed below:

Phase 1: Gelling	the sample becomes clear in color and flowable.
Phase 2: Creaming	the sample becomes more viscous, is white in color, and sticky.
Phase 3: Absorption	the sample becomes clear in color and has a glossy smooth finish. There is no visible residue left on the skin after absorption.

The process of treatment application will take at least 10 minutes each and may, in some cases, take up to 15 mins to complete for each periorbital region. After the last drop as been applied to the skin, it is critical that the product is continually rubbed onto the skin until all 3 phases has been observed for the last time, especially the creaming phase. This procedure will be completed when there is no liquid visible on the surface of the skin.

This procedure will be employed for both, the right and left periorbital regions. The start and finish time will be recorded in the eCRF. The study medication kit drug label will be completed and peeled-off for application in the subject's Case Report Form.

4.3 Drug Storage and Drug Accountability

4.3.1 Drug Storage

The investigator will ensure that the investigational product is stored in appropriate conditions in a secure, locked refrigerator with controlled access. Until ready for dispensing, the investigational product will be stored at a controlled temperature of +5°C. Temperature logs will be maintained to document that the storage temperature has not deviated from the recommended range. Should a deviation occur in the storage temperature of unopened investigational product kits, the investigator will complete and submit an Investigational Product Deviation Report form by e-mail or fax to the Sponsor. The Sponsor will review the information submitted and will provide direction regarding further use of the applicable kit/s.

4.3.2 Drug Accountability

The principal investigator at each site is responsible for maintaining accurate records of the receipt and application of all investigational materials. The investigator may apply the investigational drug only to eligible subjects enrolled in the study. All applications of the investigational drug will be conducted at the study sites.

Eirion Therapeutics will provide drug accountability forms to assist the investigator in maintaining current and accurate inventory records covering receipt, application, and the return of investigational drug supplies. When a shipment is received, the investigator or designee will verify the quantities received. The Case Report Form includes the identification of the person to whom the drug is applied, the date of application, and any returned or unused drug. These records will be readily available for inspection by the Sponsor or a monitor and are open to any other regulatory authority inspection at any time.

When the supplies are returned, the investigator, designee, or monitor signs the investigational drug return log to verify that all used, unused, or partially used supplies have been returned, and that no study supplies remain in the investigator's possession. One copy of all inventory records and the return statement are retained by the investigator for the study files.

At study termination, unless otherwise specified, all used, unused, and partially used drug supplies should be returned to the distribution center. The study drug return form will be returned to Eirion Therapeutics, Inc., and a copy will be maintained on site.

5 SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

The study will enroll adult female subjects diagnosed with mild to severe Crow's Feet.

5.1 Inclusion Criteria

- able to understand and give written informed consent
- females 25 - 65 years of age
- willing to have facial pictures taken per protocol
- minimal to moderate Crow's Feet wrinkles (IGA 1-3) at rest
- moderate to severe Crow's Feet (IGA 3-4) on contraction
- moderate to severe Crow's Feet (SSA 3-4) on contraction
- Have adequate vision without the use of eyeglasses to assess facial wrinkles in a mirror (contact lenses are OK)
- willingness to refrain from the use of facial fillers, retinoids, botulinum toxins, laser treatments, or any product affecting skin remodeling or that might cause an active dermal response during the course of the study
- female subjects must have a negative urine pregnancy test and be non-lactating at the Baseline visit
- female subjects of child bearing age must utilize one of the following methods of birth control throughout the study: IUD, diaphragm, a condom, a spermicidal gel or foam, oral contraceptives (provided subject has been utilizing this method for at least 3 months prior to baseline and has not changed the brand within this period), or patch, injectable, implantable, or vaginal ring contraceptives. Subjects may also participate if they are surgically sterilized (tubal sterilization or hysterectomy) or are in menopause.
- subjects should be in good general health as determined by the investigator and free of any disease that may interfere with study evaluations or the Investigational Product

5.2 Exclusion Criteria

- history of adverse reactions to any prior botulinum toxin treatments
- history of vaccination with botulinum toxin
- history of non-response to any prior botulinum toxin treatments
- botulinum toxin treatment in the prior 6 months
- history of periocular surgery, brow lift or related procedures
- soft tissue augmentation or any procedures affecting the lateral canthal region in the prior 12 months
- dermabrasion or laser treatment in the periocular region in the last 6 months
- topical prescription-strength retinoids in the prior 3 months to the treatment area
- application of any topical prescription medication to the treatment area within 14 days prior to treatment
- subjects on clinically significant, concomitant drug therapy (See section 5.3 below).
- present or history of neuromuscular disease, eyelid ptosis, muscle weakness or paralysis
- present or history of “dry eye”
- systemic aminoglycoside use in the week prior to treatment application
- participation in another investigational drug trial or receiving any investigational treatment(s) within 30 days of Baseline
- alcohol or drug abuse within the past 3 years
- female subjects who are pregnant or are nursing a child
- psychiatric disease interfering with the subject’s ability to give informed consent
- refusal or inability to comply with the requirements of the protocol for any reason

5.3 Concomitant Medication

Any prescription or over-the-counter medication taken during the study will be recorded in the appropriate section of the Case Report Form.

The following medications are prohibited:

- Botulinum toxin containing products for the course of the study
- The use of any facial fillers, laser treatments, or any product affecting skin remodeling for the course of the study
- Dermabrasion or laser treatment in the periocular region for the course of the study
- Topical prescription-strength retinoids in the periocular region for the course of the study
- Tanning booths or sun exposure for the treatment day and the following 2 days
- Any topical medications applied to the treatment area for the day of treatment and 5 days following treatment. Toiletry and make-up are permitted.

- Systemic aminoglycosides for the day of treatment and 7 days following the treatment application at the Baseline Visit
- Investigational medications or treatments within 30 days of Baseline and during the course of the study

5.4 Subject Withdrawal or Removal From Study

As stated in the Informed Consent, all subjects reserve the right to withdraw from the study at any time. An effort will be made to determine why a subject discontinues the study prematurely. The reason for study discontinuation will be recorded in the eCRF. All subjects who terminate the study early and have completed the Baseline Visit will be encouraged to complete Week 26/End of Study procedures.

Any subject found to have entered the study in violation of this protocol may be withdrawn from the study after discussion with the sponsor. Any subject who requires the use of an unacceptable concomitant medication may be withdrawn from the study. The investigator will discontinue any subject from the study if, in the investigator's opinion, it is not in the subject's best interest to continue.

If the reason for withdrawal is an AE/ SAE, the specific event will be recorded and every effort will be made by the Investigator to document the outcome. The date that the subject is withdrawn from the study and the reason for discontinuation will be recorded on the Case Report Form. Subjects who discontinue from the study or who are lost to follow up will not be replaced.

5.4.1 Subject Unblinding Procedures

Randomization lists will be maintained by the sponsor. In case of serious adverse events or other medical emergencies that make it necessary to unblind the treatment code for a specific subject, the investigator will, after consultation with the sponsor, submit a written request for unblinding to the Medical Monitor. The request will be documented, and the applicable information will be sent to the investigator via fax or e-mail. Unblinded subjects will be discontinued from the study.

6 STUDY PROCEDURES

6.1.1 Baseline (Qualifying) Visit

Prior to participating in any aspect of the study, each subject will be fully informed, both verbally and in writing, of the conduct and consequences of the study. Each subject must

sign the written Informed Consent prior to the conduct of the Baseline (Qualifying) evaluation.

The investigator will assign a unique identification code to each subject being evaluated for participation in the trial. The following procedures will be conducted:

- using the rating guide provided in Appendix A, record right and left Investigator's Global Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- using the same rating guide provided in Appendix A, record right and left Subject's Self-Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- record medical history and concomitant diseases
- record concomitant medication usage
- record history of botulinum use
- female subjects of child-bearing potential will be given a urine pregnancy test
- assess eligibility according to the Inclusion and Exclusion criteria in 5.1 and 5.2

If the subject is deemed eligible to participate in the study, the subject will be randomized and treated.

- record vital signs (weight, height, temperature, resting pulse and blood pressure, and respiration rate)
- collect non-fasting blood samples for laboratory safety testing
- record and transmit a 12-lead ECG
- take color photographs (see Appendix C for photograph procedure)
- evaluate for muscle weakness (ocular and the extremities) or difficulty swallowing or breathing (Signs of Botulinum Toxin Spread, Appendix B)
- provide the study medication with the lowest available Kit No. to the investigator.
- apply skin-preconditioning using the Dermaroller
- Investigator will apply the topical treatment to the left and right lateral canthal areas
- record subject's experience with the application process
- evaluate for topical adverse event reactions 30 minutes after application using the Irritation Score in Appendix D
- instruct the subject to avoid sun exposure or tanning beds for two days after treatment
- instruct the subject to avoid strenuous activities on the day of application which will cause them to perspire
- instruct the participant not to touch or let others touch the treatment area until the treatment area is washed with soap and water

- instruct the participant to wash the treatment areas with soap and water no sooner than 12 hours after treatment application but no later than 24 hours after treatment application
- schedule follow-up appointment for the next office visit

6.1.2 Week 1 Visit (+/- 2 days)

The Week 1 visit will occur one week post Baseline (+/- 2 days):

- ask the open ended “How Do You Feel” question and document answer in the electronic Case Report Form
- if the subject noted any change in well-being since last investigator contact, document details on the Adverse Event eCRF
- record changes in medication usage from the Baseline (Qualifying) visit
- record vital signs (weight, temperature, resting pulse and blood pressure, and respiration rate)
- ask if the subject experienced weakness, lethargy, or difficulty swallowing or breathing
- evaluate for muscle weakness (ocular and the extremities) or difficulty swallowing or breathing (Appendix B)
- using the rating guide provided in Appendix A, record right and left Investigator’s Global Assessment score of Crow’s Feet, both, “at rest” and “on contraction”
- using the same rating guide provided in Appendix A, record right and left Subject's Self-Assessment score of Crow’s Feet, both, “at rest” and “on contraction”
- take color photographs (see Appendix C for photograph procedure)
- schedule the subject for the next office visit

6.1.3 Week 2 Visit (+/- 3 days)

The Week 2 visit will occur two weeks post Baseline (+/- 3 days).

- ask a non-leading “How Do You Feel” question and document answer in the electronic Case Report Form
- if subject noted any change in well-being since last investigator contact, document details on the Adverse Event eCRF
- record changes in medication usage
- record vital signs (weight, temperature, resting pulse and blood pressure, and respiration rate)
- ask if the subject experienced weakness, lethargy, or difficulty swallowing or breathing

- evaluate for muscle weakness (ocular and the extremities) or difficulty swallowing or breathing (Appendix B)
- record and transmit a 12-lead ECG
- using the rating guide provided in Appendix A, record right and left Investigator's Global Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- using the same rating guide provided in Appendix A, record right and left Subject's Self-Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- take color photographs (see Appendix C for photograph procedure)
- schedule subject for the next office visit

6.1.4 Week 4 Visit (+/- 4 days)

The Week 4 visit will occur 4 weeks post Baseline +/- 4 days.

- ask a non-leading "How Do You Feel" question and document answer in the electronic Case Report Form
- if subject noted any change in well-being since last investigator contact, document details on the Adverse Event Form
- record changes in medication usage
- record vital signs (weight, temperature, resting pulse and blood pressure, and respiration rate)
- ask if the subject experienced weakness, lethargy, or difficulty swallowing or breathing
- evaluate for muscle weakness (ocular and the extremities) or difficulty swallowing or breathing (Appendix B)
- using the rating guide provided in Appendix A, record right and left Investigator's Global Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- using the same rating guide provided in Appendix A, record right and left Subject's Self-Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- take color photographs (see Appendix C for photograph procedure)
- collect non-fasting blood samples for laboratory safety testing
- female subjects of child-bearing potential will be given a urine pregnancy test
- schedule subject for the next office visit

6.1.5 Week 8 Visit (+/- 7 days)

The Week 8 visit will occur 8 weeks post Baseline +/- 7 days.

- ask a non-leading "How Do You Feel" question and document answer in the electronic Case Report Form

- if subject noted any change in well-being since last investigator contact, document details on the Adverse Event Form
- record changes in medication usage
- record vital signs (weight, temperature, resting pulse and blood pressure, and respiration rate)
- using the rating guide provided in Appendix A, record right and left Investigator's Global Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- using the same rating guide provided in Appendix A, record right and left Subject's Self-Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- take color photographs (see Appendix C for photograph procedure)
- schedule subject for the next office visit

6.1.6 Week 12 Visit (+/- 7 days)

The Week 12 visit will occur 12 weeks post Baseline +/- 7 days.

- ask a non-leading "How Do You Feel" question and document answer in the electronic Case Report Form
- if subject noted any change in well-being since last investigator contact, document details on the Adverse Event Form
- record changes in medication usage
- record vital signs (weight, temperature, resting pulse and blood pressure, and respiration rate)
- using the rating guide provided in Appendix A, record right and left Investigator's Global Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- using the same rating guide provided in Appendix A, record right and left Subject's Self-Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- take color photographs (see Appendix C for photograph procedure)
- schedule subject for the next office visit

6.1.7 Week 18 Visit (+/- 7 days)

The Week 18 visit will occur 18 weeks post Baseline +/- 7 days.

- ask a non-leading "How Do You Feel" question and document answer in the electronic Case Report Form
- if subject noted any change in well-being since last investigator contact, document details on the Adverse Event Form
- record changes in medication usage
- record vital signs (weight, temperature, resting pulse and blood pressure, and respiration rate)

- using the rating guide provided in Appendix A, record right and left Investigator's Global Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- using the same rating guide provided in Appendix A, record right and left Subject's Self-Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- take color photographs (see Appendix C for photograph procedure)
- schedule subject for the next office visit

6.1.8 Week 26 Visit (+/- 7 days)

The Week 26 visit will occur 26 weeks post Baseline +/- 7 days.

- ask a non-leading "How Do You Feel" question and document answer in the Case Report Form
- if subject noted any change in well-being since last investigator contact, document details on the Adverse Event Form
- record changes in medication usage
- record vital signs (weight, temperature, resting pulse and blood pressure, and respiration rate)
- using the rating guide provided in Appendix A, record right and left Investigator's Global Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- using the same rating guide provided in Appendix A, record right and left Subject's Self-Assessment score of Crow's Feet, both, "at rest" and "on contraction"
- take color photographs (see Appendix C for photograph procedure)

6.1.9 Study Exit / Early Termination

The scheduled Study Exit is at Week 26. However, if a subject should discontinue prematurely, the following will be performed in addition to the procedures scheduled for the patient's terminating visit:

- collect non-fasting blood samples for laboratory safety testing

6.1.10 Unscheduled Visits

The subject may contact the investigator or may be called in for additional unscheduled visits due to safety reasons or at the discretion of the investigator or Sponsor. All unscheduled visits will describe the reason for the visit in the electronic Case Report Form. Some of the procedures that may be completed at an Unscheduled Study Visit are as follows:

- Review of adverse events and concomitant medications
- Vital signs
- Collection of blood samples for laboratory safety testing
- Urine pregnancy testing

7 STUDY DURATION AND CONDUCT

7.1 Conduct of Study

This study will be conducted in compliance with the protocol approved by the Institutional Review Board and according to Good Clinical Practice standards. No intentional deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

7.2 Duration of Study

Subject enrollment will take approximately one month. The total study duration will be approximately 7-8 months.

Each subject will participate for up to 26 weeks. There will be a (Qualifying) Baseline Visit on Week 0 and seven in-office visits at Week 1, 2, 4, 8, 12, 18, and 26.

7.3 Stopping Rules

The study is designed as a sequential, overlapping cohort, dose-escalation trial. Enrollment will be halted after each cohort until a safety review has been completed.

- Enrollment will be halted in the event that one serious adverse event (SAE), considered to be probably or definitely related to the administration of study medication, is observed.

- Enrollment will be halted in the event that one AE is observed considered to be indicative of distant spread of study medication or unintended exposure to other beings.

- The Sponsor may stop the study in its entirety or discontinue individual study centers at its discretion for any reason or, e.g. if it is observed that the protocol or sound clinical practices are not being followed, or for any other reasons.

The study protocol calls for only one single application of study medication at Baseline (Week 0). Since there is no continuous treatment, no stopping rules for subjects are

applicable and subjects will be encouraged to participate in the study until the scheduled termination visit at Week 26.

7.4 Monitoring for subject compliance

In this study, a single application of study medication at Day 0 is planned. The study medication will be applied by the Investigator or a designated healthcare professional thereby ensuring compliance with the study application procedure.

Subjects will be queried with regards to concomitant medication at all study visits.

8 ADVERSE EVENT REPORTING

Adverse event reporting will be handled in accordance with the IRB requirements and the requirements of other regulatory authorities that may apply, e.g. the Food and Drug Administration.

Adverse Events reporting will be solicited by non-leading "How Do You Feel" questions. Subtle symptoms of local or systemic spread of toxin effect would be unlikely to be recognized by the subjects as related to treatment. Therefore, study participants will be asked if they experienced weakness, lethargy, or difficulty swallowing or breathing. In addition, information derived from change in concomitant medications, laboratory analyses, and clinical observations will be evaluated for possible indications for side effects. Adverse events resulting from concurrent illnesses or reactions to concurrent medications will also be recorded. The Investigator must monitor the condition of the subject throughout the study from the time of obtaining informed consent until the final study visit.

Any adverse event, including both observed and volunteered problems, complaints, and symptoms, will be recorded on the Adverse Event pages of the electronic Case Report Form. When an adverse event occurs, the following information and assessments should be recorded in the adverse event section of the eCRF:

- The signs, symptoms or diagnosis or the event,
- The date and time of onset of the event using the 24-hour clock where midnight is 00:00 and noon is 12:00. Onset is the date when the first sign or symptoms were first noted.
- Date of recovery/ resolution
- The adverse event severity/ intensity using the criteria outlined in Section 8.1.2
- The relationship of the event to the study drug as outlined in Section 8.1.1

- Any other actions required such as therapy, medication, treatment or diagnostic procedure
- Seriousness of the event using the criteria outlined in Section 8.1.3
- Outcome (recovered, recovered with sequelae, not yet recovered, death)

Follow-up of a subject should be conducted until resolution of the adverse event or until the medical condition is stable. The investigator is responsible for the appropriate medical management of all adverse events.

Adverse events will be analyzed and reported after unblinding of the treatment code within the clinical study report. Serious Adverse Events (SAEs) will be reported by the Sponsor within 10 working days to the IRB as well as the regulatory agency, FDA. In addition, any unanticipated problems involving risk to subjects or others, which in the opinion of the local investigator was unanticipated, serious AND at least possibly related to the research procedures will be reported by the Sponsor to the IRB within 10 working days.

8.1 Definitions

An adverse event is an undesirable or unintentional event affecting the well-being of a subject that occurs during use of the study drug, whether or not considered related to the drug; this includes accidental injuries, reasons for any change in medication (drug and/or dose), and reasons for surgical procedures. It is to be noted that procedures are not adverse events. Abnormal laboratory values or clinically significant changes in laboratory values are not adverse events, but the underlying reasons are. Regardless of the severity or relationship to the investigational drug, all adverse events occurring during the study period must be recorded in the subject's eCRF.

An unexpected adverse event is one that has not been previously observed, or one that is of a specificity or severity not consistent with the current Investigator Brochure.

8.1.1 Relationship to Study Drug

The following definitions to assess the causal relationship between an adverse event and the study drug should be used:

Not Related: The event is clearly related to other factors such as a subject's clinical state, therapeutic interventions or concomitant medications.

Possibly Related: The event has a reasonable temporal relationship to study drug administration and follows a known response pattern to the study drug. However, a potential alternate etiology may be responsible for the event.

Related: The event follows a clear-cut temporal sequence from the time of drug administration and follows a known response pattern to the study drug and either occurs immediately following study drug administration, or improves on stopping the drug, or reappears on repeat exposure.

8.1.2 Adverse Event Severity

Mild: A mild adverse event is one that the symptoms are barely noticeable to a subject. It does not influence performance or prevent a subject from carrying on with normal life activities.

Moderate: A moderate adverse event is one that the symptoms make the subject uncomfortable and causes some impairment to normal life activities. Treatment for symptom(s) may be required.

Severe: A severe adverse event is one that the symptoms cause severe discomfort to the subject and severely limits the subject's normal daily activities. Treatment for symptom(s) is given.

Note that "serious" and "severe" are not synonymous. A serious adverse event must fulfill the requirements listed in the definition below, see section 8.1.3.

When intensity changes or occurs more frequently than once a day, the maximum intensity for the event will be listed. If the intensity category changes over a number of days, then these mini-events or changes will be recorded separately (i.e., having distinct onset days).

8.1.3 Serious Adverse Events

A serious adverse event is an event that is:

- fatal / results in death
- life-threatening
- results in persistent or significant disability/incapacity
- requires or prolongs subject hospitalization or
- is a congenital anomaly or birth defect

Life Threatening is defined as an event in which a subject is at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it was more severe.

Death: The death of an enrolled subject is not an event, but an outcome. It is the event that resulted in a fatal outcome that must be reported.
Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

ANY SERIOUS ADVERSE EVENT, INCLUDING DEATH DUE TO ANY CAUSE, WHICH OCCURS DURING THIS INVESTIGATION, WHETHER OR NOT RELATED TO THE STUDY MEDICATION, MUST BE REPORTED **IMMEDIATELY** (DURING NORMAL BUSINESS HOURS, 9 AM TO 5 PM, ET) TO THE SPONSOR/MEDICAL MONITOR.

Any serious adverse event should be reported to Eirion Therapeutics by telephone and e-mail within 24 hours of the event. The call should be followed-up with the completion of the written SAE report form within five days of receiving firsthand knowledge of the event. Full details of the event, any sequelae and an assessment of the relationship to the study drug must be provided in the report. Any serious adverse event must also be reported to the Institutional Review Board within 48 hours of receiving firsthand knowledge of the event and a copy of this SAE report must be sent to Eirion Therapeutics. The original SAE report form should be maintained in the Regulatory Binder. It is the Sponsor's responsibility to fulfill reporting obligations to the FDA.

Reports of serious adverse events should be made by telephone to:

Eirion Therapeutics Clinical Development Department: 215-356-7532
or 610-247-6246

Serious adverse events associated with the use of the study medication will be reported to appropriate regulatory agencies, investigators, and the IRB by the Sponsor.

8.1.4 Unanticipated Problems Involving Risk to Subjects or Others

Unanticipated problems involving risk to subjects or others are:

- Any serious event (including on-site and off-site adverse events, injuries, side effects, deaths or other problems) which in the opinion of the local investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
- Any serious accidental or unintentional change to the IRB-approved protocol that involves risk or has the potential to recur.
- Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
- Any breach in confidentiality that may involve risk to the subject or others.
- Any other serious and possibly related event which in the opinion of the investigator constitutes an unanticipated risk.

8.2 Adverse Event Follow-up

Adverse events and Serious Adverse Events will be followed up until their resolution or until a stable outcome has emerged.

8.2.1 Pregnancy

Every effort must be made to avoid pregnancy during the study. If pregnancy does occur, Eirion Therapeutics must be informed immediately. The mother and fetus must be followed until the birth of the infant. In general, the follow up will include the course, duration, and outcome of the pregnancy, and the infant outcome. As the investigational product is applied only once during the study, subjects having a positive urine pregnancy test at or after the Week 4 Visit will be permitted to remain in the study.

Medically accepted methods of birth control are surgical sterilization (tubal sterilization or hysterectomy), vaginal ring contraceptive, patch contraceptive, injectable contraceptive, implantable contraceptive, Intrauterine Device (IUD), diaphragm, condom, or spermicidal gel or foam. Oral contraceptives (prescribed birth control pill) are also acceptable provided this method has been used for at least 4 months prior to the qualifying visit with no change of the brand within this period.

9 STATISTICAL PLAN

9.1 Subject Population(s) for Analysis

9.1.1 Sample size

This study is powered based on the interim results of studies LCL-206 and 207.

9.1.2 ITT and PP population

Statistical analysis of efficacy will be performed on the ITT population of all treated subjects with at least one post-baseline visit, including those for whom only incomplete data are available.

Where data are missing due to subject discontinuation or other reasons, the last post-baseline observation carried forward (LOCF) procedure will be used for each post-baseline visit with missing data. The exception to this procedure will be the treatment of missing data only on one side of the face, as discussed below. Subjects who are lost to follow-up and who do not have at least one post-baseline visit will not be included in the analysis.

An additional analysis may be performed in the per protocol population. Subjects will be considered “per protocol” if they complete the final visit evaluation without a major protocol violation. No data imputations will be made for this analysis.

9.2 Statistical Methods

9.2.1 Study Population

Descriptive statistics will be used to summarize demographic characteristics (age, gender, race, height and weight) and background characteristics for all randomized subjects by treatment group. Past/coexistent medical history information for all randomized subjects will be presented in a by-subject listing. Baseline assessments of LCL severity will also be presented as background characteristics of the population and summarized by treatment group.

Demographic data will be summarized using descriptive statistics. Categorical measures will be summarized by counts and percentages. Continuous measures will be summarized with means, standard deviations and ranges (min and max).

Descriptive statistics will be used to summarize study medication compliance and exposure for all randomized subjects. Prior and concomitant medication information for all enrolled subjects will be presented in a by-subject listing.

9.2.2 Primary Efficacy Analysis

The IGA and SSA scores (Crow’s Feet Wrinkle scale) are evaluations performed by the investigator and the subject, respectively, measured both at rest and on contraction. For analysis purposes they will be averaged between left and right sides prior to analysis. In the event one side has missing data for a visit, the result from the side with non-missing data will be used instead of an average value. These scores will be treated as continuous measures for calculating means and performing ANOVA analyses, and they will be used as described below to derive binary indicators of treatment success, which will be analyzed as dichotomous measures.

Efficacy analyses will be based on the assessments from the treatment areas, i.e. the lateral canthal area only. Alpha will be set at 0.05 using two-tailed tests. The Crow’s Feet Wrinkle scale is an ordinal categorical scale ranging from 0 to 4. As described above, left- and right-side values will be averaged, and the averaged values will be used for analysis.

The Investigator’s Global Assessment (IGA) is the primary efficacy parameter, and the evaluation of each active drug group vs. vehicle will be the primary comparisons. A comparison between the two active drug groups will also be performed, along with a

comparison between the two active drug groups pooled vs vehicle. Results will be summarized for each treatment group and at each visit using frequency distributions.

For the primary efficacy analysis, "IGA on contraction" (IGA-C) data will be analyzed at each visit to evaluate the proportion of patients achieving treatment success (responder). For this analysis, a response will be defined as a reduction from baseline in IGA-C by at least 2 points. A separate chi-square test will be used to evaluate the effect of each dose of ET-01 compared to Vehicle. A chi-square test will also be performed evaluating the overall effect of active drug vs vehicle by collapsing the two active drug treatment groups for this analysis. In addition, a separate chi-square test will be used to compare the two active drug groups. The ITT population will be used for this analysis.

9.2.3 Secondary Efficacy Analyses

The ITT population will be used for the secondary analyses. As a secondary efficacy analysis, data will be analyzed at each post-baseline visit to evaluate the proportion of patients achieving a composite treatment success, defined as a response on both the IGA-C and SSA-C scales. The analysis models for the primary efficacy analysis will be used.

Treatment success based on the SSA alone will also be analyzed using the above definition and analysis models.

In addition, mean change from Baseline IGA will be analyzed using an analysis of variance (ANOVA) model. The first model contrasts will be separate evaluations of the effect of each active group vs. vehicle. Additional contrasts will be performed comparing pooled active treatment groups vs. vehicle and comparing the two active treatment groups. Contrasts will be made within the ANOVA model using LSMeans and the appropriate pooled error term, with no alpha adjustment for multiple comparisons. An analysis of covariance (ANCOVA) model with baseline average IGA score as the covariate will be used if it yields greater sensitivity than the ANOVA model.

A similar model will be used to analyze mean change from baseline SSA.

Primary and secondary analyses will also be performed based on IGA and SSA evaluations made at rest.

9.2.4 Safety Analysis

The assessment of safety will be based mainly on the frequency of adverse events. Other safety data (e.g., vital signs and special tests) will be summarized as appropriate.

Adverse events will be coded using a current MedDRA dictionary and summarized by presenting, for each treatment group, the number and percentage of subjects having any adverse event, having an adverse event in each body system (System Organ Class), and having each coded individual adverse event. Other adverse event information collected (e.g., severity/intensity or relationship to study medication) will be listed as appropriate.

Data from other tests will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. No inferential statistical tests are planned for safety data but may be performed on an ad-hoc basis to highlight any comparisons that may warrant further consideration.

9.2.5 Interim Analysis

Interim analyses for efficacy and safety may be conducted after all subjects have passed the Week 4 visit. As there is only one treatment at Baseline and, therefore, interim analyses will not alter the conduct of the trial, no alpha adjustment will be required.

9.3 Significance

Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

9.4 Termination Criteria

Enrollment into the study will be halted as described in section 7.3 Stopping Rules. No other type of interim analysis is planned that could trigger termination of the trial.

9.5 Deviation Reporting

A Statistical Analysis Plan will be created prior to the completion of the study and unblinding of the database. Any deviations from or additions to the statistical analyses specified in the protocol will be described and justified in the Statistical Analysis Plan.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Data reflecting subject experience with the drug under investigation will be recorded on appropriate source documents and in the eCRF. The investigator understands that the office and hospital records of subjects entered in this study will be required to be available to copying and inspection if requested by a properly authorized employee of the Sponsor or the Department of Health and Human Services, under the supervision of the investigator or a designated representative and in accordance with Federal regulations.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The investigator will allow Eirion Therapeutics or their designated affiliates to periodically audit, at mutually convenient times during the study and after the study has been completed, all source documents and corresponding portions of office, hospital, and laboratory records of each subject. The monitoring visits will provide Eirion Therapeutics with the opportunity to confirm the rights and safety of the subjects, ensure the confidentiality of the data and subject's identification, evaluate the progress of the study, verify the accuracy and completeness of the eCRFs, assure compliance with protocol requirements, applicable FDA regulations, IRB and ICH-GCP Guidelines, confirm that investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records. The sponsor may stop the study if it is observed that the protocol or sound clinical practices are not being followed.

12 ETHICAL CONSIDERATIONS

This study must be approved by an IRB or other ethical approval body prior to subject enrollment. The governing IRB must comply with all the requirements set forth in 21 CFR § 56. The IRB is responsible for the initial approval, any amendments, advertisements, and continuing review of the proposed clinical study. The IRB will review any written materials given to the subject and the Informed Consent Forms. The investigator must retain a copy of the approval letter that contains the study number, protocol title and identification of all documents approved. A copy of the letter must be sent to the sponsor prior to drug shipment to the investigator.

The investigator agrees to promptly report to the IRB all unanticipated problems involving risks to human subjects or others.

The investigator will ensure that this study is conducted in full conformity with the principles of the "Declaration of Helsinki" and with the laws and regulations of the participating countries, whichever affords the greater protection to the individual. It is the responsibility of the investigator to obtain informed consent in written form (according to local legal requirements) from each subject participating in this study. All subjects will be informed of the aims, methods, anticipated benefits, potential hazards and confidentiality of data. Candidates will also be told that they are free to refuse participation or withdraw from the study at any time. A consent form must be signed and dated by the subject before he/ she is exposed to any study-related procedure, including screening tests for eligibility. The subject will receive a copy of the signed consent. The subject should be informed if new information becomes available that may be relevant to his/ her willingness

to continue participation in the study. Each subject will be informed that the monitor, in accordance with applicable regulatory requirements, may review his/ her medical records and data.

Periodic status reports must be submitted at least yearly to the IRB. Within three months after completion or termination of the study, a final report should be submitted to the IRB and the Sponsor. The investigator must maintain an accurate and complete record of all submissions made to the IRB including a list of all reports and documents submitted.

The investigator is responsible for maintaining all the records which enable the conduct of the study at the site to be fully understood in compliance with the ICH-GCP filing standard. The investigator is responsible for the completion and maintenance of the confidential subject identification code which provides the sole link between named subject source records and the eCRF data. The investigator must arrange for the retention of study records for 5 years after the completion of the study. No study site files may be destroyed without prior written agreement between the investigator and the sponsor. Should the investigator elect to assign the study documents to another party or move them to another location not noted on the FDA 1572 Form, the sponsor must be notified.

13 DATA HANDLING AND RECORD KEEPING

Data reflecting subject experience with the drug under investigation will be recorded in the eCRF. Sites may use a print-out of the eCRF or their own record keeping system as source documentation. After monitoring, source verification and authentication by the Principal Investigator, the eCRF will be locked. The study specific data in the eCRF are the sole property of the Sponsor.

It is the Investigator’s responsibility to ensure completion and to review and approve all data in the eCRF and source documents. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the eCRF and source document.

All fields and blanks must be completed or marked intentionally blank as appropriate following the instructions on the eCRF. eCRFs will be electronically signed and dated by the investigator or a designated representative. If an entry on an eCRF already submitted requires change, the Electronic Data Capture (EDC) system will capture the reason for the change and then the correction will be made according to the procedures dictated by the EDC system.

The investigator will maintain adequate records for the study including subject's eCRFs, medical records, laboratory reports, informed consent forms, drug accountability records, safety reports, information regarding subjects who discontinued, and any other pertinent data.

14 FINANCE

The study will be sponsored by Eirion Therapeutics, Inc.

15 INVESTIGATOR'S AGREEMENT

I have read Eirion Therapeutics' protocol entitled: "Clinical Trial to Evaluate ET-01 in Subjects with Lateral Canthal Lines" in conjunction with the "Investigators Drug Brochure" which contains all information necessary to the conduct of the study. I agree to conduct the study as outlined therein and according to ICH Good Clinical Practice.

Investigator's Signature	Date
Sponsor's Signature Klaus Theobald, MD, PhD Chief R&D Officer Eirion Therapeutics, Inc.	Date

16 REFERENCES

Ascher, Benjamin; Rzany, Berthold; Grover, Rajiv
Efficacy and Safety of Botulinum Toxin Type A in the Treatment of Lateral Crow's Feet: Double-Blind, Placebo-Controlled, Dose-Ranging Study
Dermatol Surg 35:1478-1486, 2009

Carruthers, Alastair; Carruthers, Jean; Hardas, Bhushan; Kaur, Mandeep; Goertelmeyer, Roman; Jones, Derek; Rzany, Berthold; Cohen, Joel; Kerscher, Martina; Corcoran Flynn, Timothy; Maas, Corey; Sattler, Gerhard; Gebauer, Alexander; Pooth, Rainer; McClure, Kathleen; Simone-Korbel, Ulli; Buchner, Larry
A Validated Grading Scale for Crow’s Feet
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Coté, Timothy; Mohan, Aparna; Polder, Jacquelyn; Walton, Marc; Braun, Miles
Botulinum toxin type A injections: Adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases
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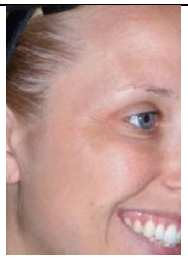
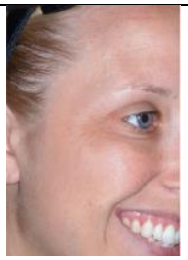
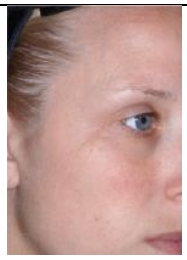
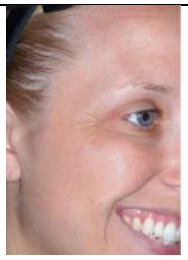
Appendix A: Crow's Feet Wrinkle Scale1

The Crow's Feet Wrinkle Scale (CFW) is a photonumeric guide that grades severity of lateral canthal lines according to one of the following five descriptions.

Score	Grade	Description	At Rest	At Smile
0	Absent	No visible wrinkles		
1	Minimal	Very fine wrinkles (that are barely visible)		
2	Mild	Fine wrinkles (that are shallow)		
3	Moderate	Moderate wrinkles (that are moderately deep)		
4	Severe	Severe wrinkles (that are severely deep)		

[1] Carruthers et. al. A Validated Grading Scale for Crow's Feet, Dermatol Surg 2008; 34:S173–S178

Investigators and subjects will use the same scale. As a photo guide, the guidance pictures shown below will be presented as 11” x 17” laminated poster cards.

Instructions for use:

For Investigators:

- “At Rest”: Ask the subject to make an expressionless face and indicate with a check mark the description that best describes his/her appearance.
- “On Contraction”: Ask the subject to make a maximally exaggerated smile and indicate with a check mark the description that best describes his/her appearance.

For Subjects:

- Place the subject in front of a mirror or provide a hand-held mirror in a well-lit room
- Provide subject with the photo guide
- “At Rest”: Ask the subject to make an expressionless face and state the grade that best describes his/her appearance. Record in the eCRF.
- “On Contraction”: Ask the subject to make a maximally exaggerated smile and using the provided scale state the grade that best describes his/her appearance. Record in the eCRF.

Appendix B: Signs of Botulinum Toxin Spread

1. Ask the subject to follow the examiner's finger with his or her eyes without moving his or her head. At eye level, the examiner should move his or her finger to the right of the subject's head and then to the left. Repeat this horizontal motion at the level of the subject's forehead and chin. Note whether there is any abnormality in the form of any inability of the subject's eyes to follow the finger.

2. Ask the subject to raise his/her eyelids. Observe any indication for "drooping".

3. Ask the subject to swallow and note any difficulty doing so.

4. Ask the subject to partially flex his or her arms at the elbow, with fist at shoulder level. Ask the subject to attempt to fully flex his or her arms against the resistance of the examiner pulling on the subject's forearms. Note whether there is an abnormality in the form of any muscular weakness.

5. Ask the subject to squat down and stand up again. Watch for any abnormalities or signs of weakness.

Appendix C: Procedure for Color Photography

Equipment: Digital Camera, Log Book, Subject-Specific Index Card

Procedure: In these clinical photographs, for the duration of the study, the only variable allowed to change is the skin condition itself. Therefore, anything extraneous to the condition (jewelry, makeup, clothing, furniture, walls, etc.) is to be eliminated from the fields to be photographed, from baseline through the final photographs. The necessity of good photos should be stressed to the subjects to ensure their cooperation. Camera, lighting, framing, and exposure must be held consistent. In the end, the pictures should read like a time-lapse movie.

Ask the subject to stand against a light background, away from any window or other source of external light. The subject should hold a white index card with his/her identification number and initials. The photographer should stand about 1 foot away from the subject and set the camera for minimum zoom and take 5 photographs: 1 full frontal face photo, and one 45° view of each of the right and left periorbital region, both, “at rest” and “on contraction”.

For the “at rest” pictures, ask the subject to have a relaxed, expressionless composure. In the frontal picture, the subject should hold an index card with subject ID, date and initials. The ID card is not required for the 45° views. For the “on contraction” pictures, ask the subject to produce a smile that is maximally exaggerated by exhorting the subject to make the biggest smile possible. An attempt should be made to consistently produce the same degree of smile in all photographs. This can be guided by observing the amount of teeth observable.

Maintain a Log Book that includes the following information:

- Protocol Number
- Investigator Name
- Subject Initials
- Subject ID Number
- Visit week
- Date of Visit
- Photographer’s Initials

At monitoring visits, the Study Monitor will upload the pictures from the camera to a laptop computer.

Appendix D: Irritation Scoring

For the irritation assessment, the following scale will be utilized:

Numeric Grades:

0 = no evidence of irritation
1 = minimal erythema, barely perceptible
2 = definite erythema, readily visible; or minimal edema; or minimal papular response
3 = erythema and papules
4 = definite edema
5 = erythema, edema, and papules
6 = vesicular eruption
7 = strong reaction spreading beyond test site

All clinically significant skin responses observed with the test products or any score of 3 or higher will be reported as an adverse event.