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CLINICAL STUDY PROTOCOL

An Open-Label Phase 2 Study to Investigate the Efficacy, Tolerability, and Safety of the HTS-519 Insert in the Treatment of Subjects with Distal Lateral Subungual Onychomycosis of the Great Toenail

IND No.	74,830
Protocol No.	HTS-002B
Version No.	3.0 (Amendment 2)
Date of Protocol	12 September 2017
Authors	[redacted]
Sponsor	Hallux, Inc. 23052 Alcalde Drive, Suite A Laguna Hills, CA 92653 United States

Confidentiality Statement:
This protocol contains information that is the property of Hallux, Inc. (Hallux) and therefore is provided to you in confidence for review by you, your staff, an applicable ethics committee/institutional review board, and regulatory authorities. It is understood that this information will not be disclosed to others without the written approval from Hallux.

This study will be conducted in compliance with Good Clinical Practice and the Declaration of Helsinki (with amendments), in accordance with local legal and regulatory requirements and in compliance with the applicable parts of the United States Code of Federal Regulations.

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1 PROTOCOL SYNOPSIS

PROTOCOL TITLE	An Open-Label Phase 2 Study to Investigate the Efficacy, Tolerability, and Safety of the HTS-519 Insert in the Treatment of Subjects with Distal Lateral Subungual Onychomycosis of the Great Toenail
PROTOCOL No.	HTS-002B
SPONSOR	Hallux, Inc.
INDICATION (PHASE)	Distal lateral subungual onychomycosis (Phase 2)
STUDY CENTERS	One investigational site in the US
INDICATION AND RATIONALE	The purpose of this study is to evaluate the efficacy, clinical benefit, and safety of the HTS-519 Insert for the treatment of subjects with laboratory-confirmed distal lateral subungual onychomycosis (DLSO) of the great toenail.
STUDY DESIGN	This is a single-center open-label study to determine the efficacy of the maximal feasible dose (MFD) of the HTS-519 Insert [redacted]
INVESTIGATIONAL PRODUCT	HTS-519 (Hallux Terbinafine Subungual) Insert, [redacted].
ROUTE AND FREQUENCY OF ADMINISTRATION	[redacted] Inserts will be administered subungually 3 times at intervals of 4 weeks (at treatment visits Days 1, 29, and 57).
STUDY OBJECTIVES	The primary efficacy objective is to provide a preliminary estimate of the rate of complete cure of DLSO at Week 48 after treatment with the HTS-519 Insert. Secondary objectives will be to provide estimates of mycological and clinical cure rates, and other responder rates. Reports of physician and subject experiences with the procedure will also be elicited as an exploratory objective. Subjects will report their pain scores during and following HTS-519 Insert placement. Physicians will assess ease of insertion. Local tolerability and safety of administration of subungual inserts will be assessed. [redacted]
PLANNED SAMPLE SIZE AND STATISTICAL CONSIDERATIONS	It is planned that at least 30 subjects will complete the 3 treatments specified. [redacted]

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PATIENT POPULATION Inclusion Criteria	1. Male or female between 18 and 74 years of age inclusive. 2. Clinical diagnosis of DLSO in at least one great toenail. If both great toenails meet inclusion criteria, the toenail with the greater involvement will be designated the target toenail. 3. Linear nail involvement of at least 4 mm, but without involvement of the proximal 3 mm of the nail, based on the investigator's visual assessment. Overall nail involvement should be at least 25% but not more than 75% as per the investigator's visual assessment (Grade 3). Nail thickness ≤ 2 mm or total thickness of the nail plus subungual debris measuring ≤ 3 mm. 4. Subject's nails are required to have a normal rate of growth (approximately 1 mm / month or greater [redacted]. 5. Laboratory confirmation of DLSO with direct microscopy of subungual debris positive for hyphal elements (KOH test) and fungal culture positive for dermatophytes. 6. Generally of good health. 7. Willing to comply with protocol requirements and sign a statement of informed consent. 8. Willing to refrain from using any lotions, creams, liquids, or polish on the large toenail or on the skin immediately adjacent to the large toenail during the treatment period unless directed to do so by the investigator. 9. Willing to refrain from using on the toenails topical products to which the subject has a high risk of developing an allergic reaction and/or dermatitis; 10. Willing to refrain from receiving pedicures for the duration of the study. 11. Willing to refrain from using topical steroids or topical antifungals on the great toenail or the skin immediately adjacent to the great toenail, or systemic antifungals for the duration of the study.
PATIENT POPULATION Exclusion Criteria	1. History of severe or chronic immunosuppression, an immunocompromised condition, known or suspected HIV, extensive dermatomycoses, extensive recurrent herpes zoster or severe dermatitis affecting the feet that would interfere with safety and tolerability assessments. 2. Any systemic or dermatologic disorder, such as uncontrolled psoriasis, severe eczema, or severe atopic dermatitis which, in the opinion of the investigator, will interfere with the study results or increase the risk of adverse events (subjects with mild, controlled psoriasis, eczema, or dermatitis may be included if the condition would not interfere with safety and tolerability assessments). 3. Any severe and/or chronic disease that would affect a subject's nail growth or interfere with the subject's ability to complete the trial, such as severe renal failure, peripheral vascular disease, severe chronic obstructive pulmonary disease, severe heart disease, uncontrolled diabetes mellitus or other endocrine disease, or uncontrolled malignancy. 4. History of toenail surgery or any significant injury to the target toenail matrix. 5. Treatment with any investigational drug within 1 month prior to Screening. 6. Topical antifungal treatment applied to the feet within 1 month prior to the start of study treatment. 7. Use of oral terbinafine within 6 months, or use of any other oral antifungal drug within 3 months, prior to the start of study treatment. 8. Hypersensitivity to terbinafine or to any other ingredients of the formulation. 9. Active onychomycosis of the fingernail. 10. Symptomatic tinea pedis requiring treatment at Day 1 of the study. 11. Superficial white, proximal subungual onychomycosis, lichen planus,

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psoriasis, or any condition that interfere with the treatment procedure or assessment of clear nail.

12. Structural deformities of the target toenail or foot (eg, genetic or pigment disorders, chemical damage, tumors) that would interfere with treatment procedures or with assessments of efficacy, safety, or tolerability.
13. Suspected subungual dermatophytoma.
14. Any other condition that in the opinion of the investigator renders the subject unsuitable for participation in this study.

EFFICACY ASSESSMENTS

Efficacy is determined in the target great toenail by

- evaluation of clinical cure (complete clearance of signs and symptoms) using the Investigator Global Assessment Scale, further documented by digital photography analysis, and
- laboratory confirmation of mycological cure (negative culture for dermatophytes and negative KOH microscopy).

From these assessments the efficacy outcomes of complete cure (mycological cure and clinical cure), mycological cure, clinical cure and effective treatment (no more than 10% affected nail) will be determined. [redacted]

SAFETY ASSESSMENTS

Safety assessments include monitoring AEs and local tolerability at the administration site using a 4-point scale. Pain assessments at time of treatment and 7-days post procedure. Results of physical examination and vital signs measurements will be assessed.

STATISTICAL METHODS

Cure rates will be estimated along with 95% confidence intervals. Interval parameters such as length and ratios will be characterized using descriptive statistics. The primary analysis population will be the intent-to-treat population. The analysis of safety is conducted in the population of all treated subjects. Rates of AEs and local tolerance assessments will be presented descriptively. Events of clinical significance will be identified individually and described without inferential statistics.

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Table 1-1 Schedule of Study Procedures

	Screening	Allocation and Treatment			Post-Treatment					
Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
	Screening	Baseline Day 1	Week 4 Day 29 ±3	Week 8 Day 57 ±3	Week 12 Day 85 ±7	Week 16 Day 113 ±7	Week 20 Day 141 ±7	Week 24 Day 169 ±7	Week 36 Day 253 ±7	Week 48 Day 337 ±7
ENROLLMENT AND SCREENING										
Informed consent	X									
Demographic, medical/medication history	X	X[a]								
Inclusion / exclusion criteria	X	X[a]								
Target toenail measurements	X	X								
INTERVENTIONS										
Notch target great toenail[b]										
[redacted]		[redacted]				[redacted]				
Administration site assessment		X	X	X						
Pain assessment		X	X	X						
ASSESSMENTS										
Physical examination and vital signs	X									X
Subungual sample for KOH microscopy and fungal culture	X[c]							X	X	X
Investigator Global Assessment of clear nail[d]	X				X	X	X	X	X	X
Digital photography[d]	X	X	X	X	X	X	X	X	X	X
Dispense subject diary		X[e]	X[e]	X[e]						
Review and record adverse events		X	X[f]	X[f]	X[f]	X	X	X	X	X
Monitor concomitant medications		X	X	X	X	X	X	X	X	X

[a] Record any change from baseline
[b] When the notch is approaching the area of the distal groove due to outgrowth of the nail, re-notch the superficial nail plate and continue measurements
[c] Subungual sampling may be repeated to confirm diagnosis of DLSO by fungal culture
[d] Nails should be clipped prior to assessments
[e] Next day follow-up call to check for adverse events, changes in medication
[f] Includes review of subject diary

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	Post-Treatment-Extension	
Procedure	**Visit 11**	**Visit 12**
	Week 60 Day 420 ±7	**Week 72 Day 504 ±7**
ENROLLMENT AND SCREENING		
Informed consent		
Demographic, medical/medication history		
Inclusion / exclusion criteria		
Target toenail measurements		
INTERVENTIONS		
Notch target great toenail[b]		
Administer study treatment		
Administration site assessment		
Pain assessment		
ASSESSMENTS		
Physical examination and vital signs		
Subungual sample for KOH microscopy and fungal culture	X	X
Investigator Global Assessment of clear nail[d]	X	X
Digital photography[d]	X	X
Dispense subject diary		
Review and record adverse events		
Monitor concomitant medications		

[a] Record any change from baseline
[b] When the notch is approaching the area of the distal groove due to outgrowth of the nail, re-notch the superficial nail plate and continue measurements
[c] Subungual sampling may be repeated to confirm diagnosis of DLSO by fungal culture
[d] Nails should be clipped prior to assessments
[e] Next day follow-up call to check for adverse events, changes in medication
[f] Includes review of subject diary

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LIST OF ABBREVIATIONS

ADL	Activities of daily living
AE	Adverse event
AR	Adverse reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
[redacted]	[redacted]
CFR	Code of Federal Regulations
[redacted]	[redacted]
CRF	Case report form
DLSO	Distal lateral subungual onychomycosis
EDC	Electronic data capture
EOS	End of Study
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HTS	Hallux Terbinafine Subungual
ICH	International Conference on Harmonization
IGA	investigator Global Assessment
IRB	Institutional Review Board
KOH	Potassium hydroxide
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum feasible dose
NRS	Numerical rating scale
OTC	Over-the-Counter (non-prescription)
PEG	Polyethylene Glycol
PK	Pharmacokinetic
[redacted]	[redacted]
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Suspected adverse reaction
SOP	Standard operating procedure
SQL	Sonora Quest Laboratories
TBF	Terbinafine
WMA	World Medical Association

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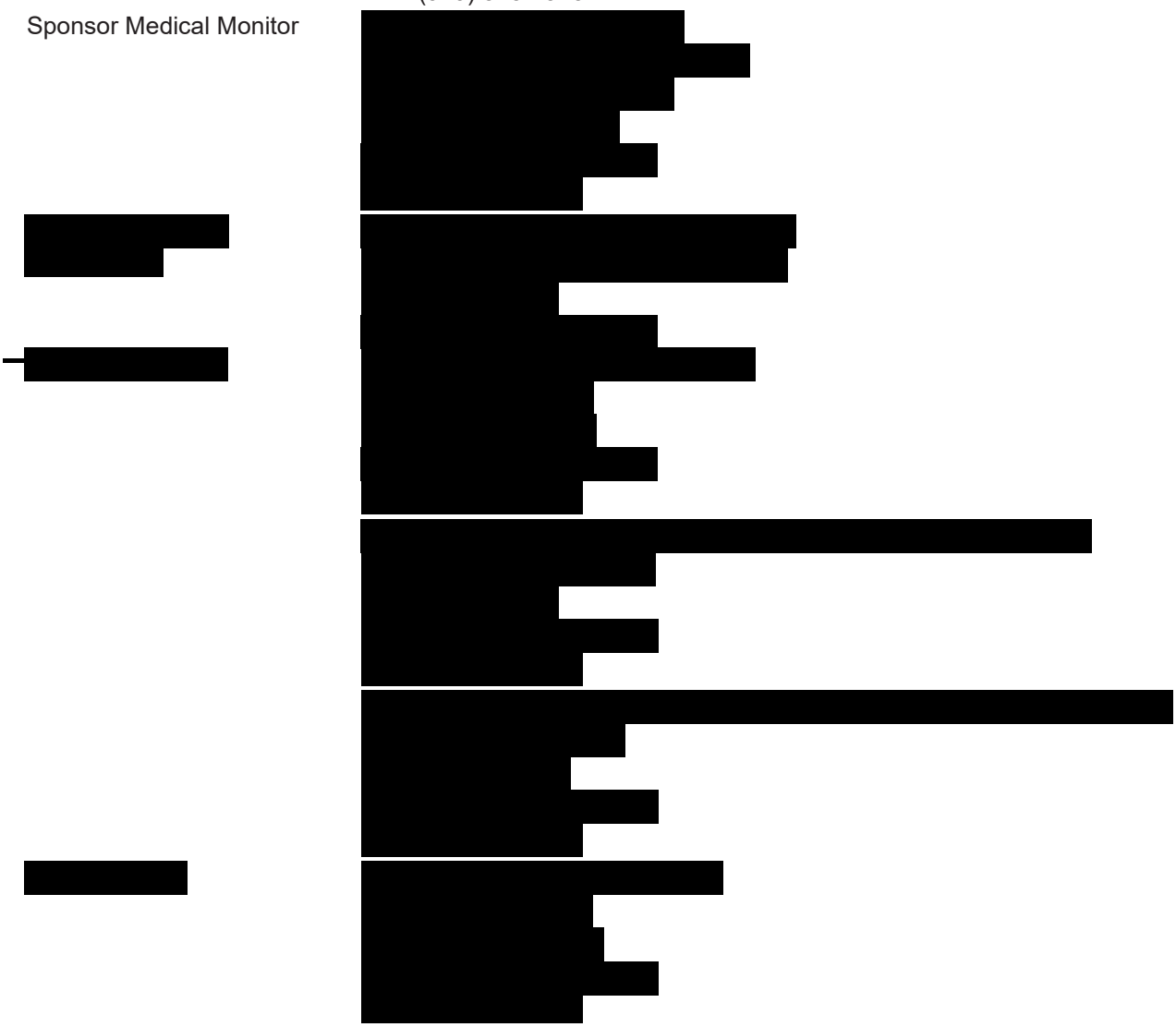
2 KEY ROLES AND CONTACT INFORMATION

Name / Role	Address
Sponsor	Hallux, Inc. (Hallux) 23052 Alcalde Drive, Suite A Laguna Hills, CA 92653 Telephone: (800) 380 9130 Fax: (949) 315 7373
Sponsor Medical Monitor	[redacted]



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3 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

3.1 Background Information

Onychomycosis or *tinea unguium* is a chronic fungal infection of the nail unit affecting 2-18% of the population worldwide. [redacted]

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[redacted]

3.2 Rationale

Hallux is developing an investigational treatment for DLSO that utilizes areas of reduced adherence between nail bed and nail plate to deliver a biodegradable insert containing the potent fungicidal terbinafine to the subungual space, targeting areas with high fungal viability, [redacted]

The HTS-519 Insert contains [redacted]

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[redacted]

Figure 3-2 Sample Location and Percentage Viable Organisms by Fungal Culture

[redacted]

3.3 Potential Risks and Benefits

Terbinafine has been approved for use as a topical agent for skin infections since 1993 and orally for the treatment of onychomycosis since 1996. Both the topical and oral formulations are generally regarded as safe and effective.

HTS-002B is the first clinical study that uses the HTS-519 Insert. [redacted].

3.3.1 Potential Risks

[redacted]

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[redacted]

The expected adverse events (AEs) are application site reactions, including pain, swelling, irritation, and hematoma; although many patients show none of these reactions. The implantation procedure in all 6 clinical trials conducted to date has been preceded by local anesthesia, either topical ethyl chloride or a lidocaine digital block. Those patients who reported post-procedural pain usually experienced discomfort within 2 days following the procedure.

[redacted]

3.3.2 Potential Benefits

Subungual administration of the HTS-519 Insert has the potential benefit of delivering the effective antifungal terbinafine in high concentrations directly to the site of infection, without systemic exposure. [redacted] The clinical effect of subungual administration of the HTS-519 Insert may deliver a complete cure rate that is at least comparable to the current gold standard.

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4 STUDY OBJECTIVES

4.1 Study Objectives

The primary efficacy objective of this study is to provide a preliminary estimate of the rate of complete cure of DLSO at Week 48 after treatment with the HTS-519 Insert. Secondary objectives will be to provide estimates of mycological and clinical cure rates, and other responder rates.

Reports of physician and subject experiences with the procedure will also be elicited as an exploratory objective. Subjects will report their pain scores during and following HTS-519 Insert placement. Physicians will assess ease of insertion. Local tolerability and safety of administration of subungual inserts will be assessed.

[redacted]

4.2 Study Outcome Measures

4.2.1 Primary

The primary outcome measure, complete cure at Visit 10 (Week 48), is based on clinical evaluation of “clear nail” using the Investigator’s Global Assessment (IGA) Scale (Section 9.1.1) and laboratory confirmation of mycological cure of the target toenail (Section 9.1.2).

The investigator will evaluate the extent of clear nail or absence of signs of residual onychomycosis using the IGA Scale (Table 4-1), with a Grade 0 representative of a clinical cure. The investigator’s assessment will be documented by digital photography planimetric analysis by Canfield Scientific, Inc.

[redacted]

Subungual samples will be assessed for KOH visualization by microscopy and fungal culture for dermatophytes by a laboratory. Since subjects enroll with both a positive KOH (fungal elements present at microscopy) and positive culture for dermatophytes, a mycological cure is declared when both laboratory assessments are negative.

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4.2.2 Secondary

The four secondary outcome measures are combinations of the same parameters used for evaluating the primary efficacy outcome of complete cure (Table 4-2).

Table 4-2 Secondary Efficacy Outcomes

Efficacy Outcome	Efficacy Criteria	
	investigator Assessment / Planimetry	**Laboratory Outcome**
Complete Cure other than at Week 48 (EOS)	Grade 0 - Completely clear nail, with nail area clear of signs of residual disease	Negative KOH microscopy and Negative culture for dermatophytes
Effective Treatment	Grade 1 - Almost clear nail with ≤ 10% affected nail	
Mycological Cure	Not a determinant in outcome	
Clinical Cure	Grade 0 - Completely clear nail, with nail area clear of signs of residual disease	Not a determinant in the outcome

4.2.3 Exploratory

Exploratory efficacy outcomes are summarized in Table 4-3.

Table 4-3 Exploratory Efficacy Outcomes

[redacted]

4.2.3.1 [redacted]

[redacted]

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5 SELECTION AND WITHDRAWAL OF PATIENTS

Subjects with a clinical diagnosis of DLSO of the large toenails caused by dermatophytes, laboratory confirmed by KOH visualization and positive culture for dermatophytes, will be enrolled until 30 subjects have completed the 3 treatments specified by the protocol.

Approximately 60 subjects will be screened for entrance to the study. Based on previous studies in this indication, it is expected that the majority of subjects will be male. Subjects will be recruited from a single podiatric practice, the [redacted]. The practice operates from additional locations [redacted] that may serve as referral (not treatment) centers.

Subjects must meet all of the following inclusion criteria (Section 5.1) to be eligible for enrollment into the study and must not meet any of the exclusion criteria listed in Section 5.2 in order to be eligible.

5.1 Subject Inclusion Criteria

1. Male or female between 18 and 74 years of age inclusive.
2. Clinical diagnosis of DLSO in at least one great toenail. If both great toenails meet inclusion criteria, the toenail with the greater involvement will be designated the target toenail.
3. Linear nail involvement of at least 4 mm, but without involvement of the proximal 3 mm of the nail, based on the investigator's visual assessment. Overall nail involvement should be at least 25% but not more than 75% as per the investigator's visual assessment (Grade 3). Nail thickness ≤ 2 mm or total thickness of the nail plus subungual debris measuring ≤ 3 mm.
4. Subject's nails are required to have a normal rate of growth (approximately 1 mm / month or greater) [redacted].
5. Laboratory confirmation of DLSO with direct microscopy of subungual debris positive for hyphal elements (KOH test) and fungal culture positive for dermatophytes.
6. Generally of good health.
7. Willing to comply with protocol requirements and sign a statement of informed consent.
8. Willing to refrain from using any lotions, creams, liquids, or polish on the large toenail or on the skin immediately adjacent to the large toenail during the treatment period unless directed to do so by the investigator.
9. Willing to refrain from using on the toenails topical products to which the subject has a high risk of developing an allergic reaction and/or dermatitis;
10. Willing to refrain from receiving pedicures for the duration of the study.
11. Willing to refrain from using topical steroids or topical antifungals on the great toenail or the skin immediately adjacent to the great toenail, or systemic antifungals for the duration of the study.

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5.2 Subject Exclusion Criteria

1. History of severe or chronic immunosuppression, an immunocompromised condition, known or suspected HIV, extensive dermatomycoses, extensive recurrent herpes zoster or severe dermatitis affecting the feet that would interfere with safety and tolerability assessments.
2. Any systemic or dermatologic disorder, such as uncontrolled psoriasis, severe eczema, or severe atopic dermatitis which, in the opinion of the investigator, will interfere with the study results or increase the risk of adverse events (subjects with mild, controlled psoriasis, eczema, or dermatitis may be included if the condition would not interfere with safety and tolerability assessments).
3. Any severe and/or chronic disease that would affect a subject's nail growth or interfere with the subject's ability to complete the trial, such as severe renal failure, peripheral vascular disease, severe chronic obstructive pulmonary disease, severe heart disease, uncontrolled diabetes mellitus or other endocrine disease, or uncontrolled malignancy.
4. History of toenail surgery or any significant injury to the target toenail matrix.
5. Treatment with any investigational drug within 1 month prior to Screening.
6. Topical antifungal treatment applied to the feet within 1 month prior to the start of study treatment.
7. Use of oral terbinafine within 6 months, or use of any other oral antifungal drug within 3 months, prior to the start of study treatment.
8. Hypersensitivity to terbinafine or to any other ingredients of the formulation.
9. Active onychomycosis of the fingernail.
10. Symptomatic tinea pedis requiring treatment at Day 1 of the study.
11. Superficial white, proximal subungual onychomycosis, lichen planus, psoriasis, or any condition that interfere with the treatment procedure or assessment of clear nail.
12. Structural deformities of the target toenail or foot (eg, genetic or pigment disorders, chemical damage, tumors) that would interfere with treatment procedures or with assessments of efficacy, safety, or tolerability.
13. Suspected subungual dermatophytoma.
14. Any other condition that in the opinion of the investigator renders the subject unsuitable for participation in this study.

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5.3 Subject Recruitment and Retention

Subjects will be primarily recruited from a single podiatric practice and 3 (non-treatment) locations that are part of the practice. [redacted]

[redacted]

5.4 Subject Withdrawal and Stopping Criteria

In accordance with legal requirements and ICH GCP, subjects may withdraw from the study at any time without stating a reason and without prejudice to further treatment. A subject's participation is to be terminated immediately upon his/her request. If, at the time of refusal, HTS-519 has already been administered, the subject will be advised on follow-up safety procedures.

The investigator may withdraw a subject from the study and discontinue study treatment and assessments at any time.

The subject and the investigator are advised to be alert to any adverse effects that may be attributable to the study medication or procedures, and not to continue study treatments when there is any perceived risk of harm to the subject.

A subject's discontinuation from the study will be considered if a subject experiences a serious adverse event (SAE) or develops conditions which would have prevented his/her entry into the study according to the safety-related medical exclusion criteria.

The investigator must discontinue a subject from the study if the following criteria are met:

- Any subject who develops intolerable adverse effects attributable to the study procedures - an "intolerable adverse effect" is one that is regarded by either the subject or the investigator or both as necessitating the discontinuation of study treatment.
- Biochemical or clinical evidence of liver injury with total bilirubin levels greater than 3 times the upper limit of normal is detected.

If a subject is discontinued because of an AE, the event will be followed until it is resolved or it is considered to have stabilized and does not require further follow-up.

If a subject is discontinued at any time after entering the study, the subject will stop receiving further treatment. The investigator will make every effort to see the subject

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and complete a final evaluation, following the end of study assessments (Section 8.3.3). This is not required if a subject is withdrawn prior to dosing.

Early discontinuation of each subject who has given informed consent to participate will be recorded in the case report form (CRF) including the primary reason for discontinuation, other than study completion, as described in Table 5-1:

Table 5-1 Reason and Description of Subject Withdrawal or Discontinuation

Reason	Description
Failure to meet eligibility criteria	Failure to meet inclusion and / or exclusion criteria
Adverse Events (AE)	Clinical events occurred or laboratory results are reported that in the medical judgment of the investigator are grounds for discontinuation in the best interests of the subject.
Lost to Follow-Up	The subject stopped coming for visits and study personnel were unable to contact the subject.
Withdrawal of Consent	The subject desired to withdraw from further participation in the study. The subject is not obliged to provide any reason for withdrawal of consent, but where a reason is given this will be recorded in the CRF.
Study Terminated by Sponsor	An indication that a clinical study was stopped by its sponsor.
Physician Decision	A position, opinion or judgment to withdraw or discontinue the subject from the study reached after consideration by a physician.
Protocol Deviation	The subject failed to adhere to the protocol requirements, and, in the investigator's opinion, the best interest of the subject or study assessment of safety of the subject would be affected by continued involvement.
Lost to Follow-Up	The subject stopped coming for visits and study personnel were unable to contact the subject.
Death	Outcome was death
Other	The subject was terminated for a reason, other than one previously listed, that could potentially impact data or subject safety.

5.5 Handling of Subject Withdrawals or Discontinuation of Study Intervention

All enrolled subjects will be included in the study analysis whether or not they withdraw from the study or discontinue the study procedures after enrollment. [redacted]

5.6 Study Discontinuation

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reasons for the termination or suspension.

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6 STUDY DESIGN

6.1 Study Design

This is a single-center, open-label study intended to establish preliminary point estimates of efficacy and assess the clinical benefits and safety of HTS-519 Insert, administered in the subungual space, in subjects with clinically and laboratory-confirmed DLSO of the great toenail.

All subjects will be screened for DLSO and will meet specific inclusion and exclusion criteria.

If both great toenails have clinical and laboratory evidence of onychomycosis and fulfill the inclusion / exclusion criteria, the one with the greater involvement will be designated as the target nail for efficacy evaluation, but both of the great toenails may be treated and evaluated for safety if the subject and the investigator consent.

Treatment will be administered to all subjects [redacted] Each subject will receive a dose [redacted] based on [redacted] nail involved by disease (Section 7.2). Each treatment visit will be followed up with a phone contact the next day to enquire about adverse events.

After the last treatment on Day 57, subjects will return for follow-up observations 4 weeks apart, until Visit 8 (Week 24). Thereafter, subjects are followed-up every 12 weeks until End of Study Visit 10 (Week 48). Study design is summarized in Table 6-1.

At Week 48, subjects that in the opinion of the investigator have a reasonable chance to reach a complete cure in the 24 weeks following the End of Study Visit or have reached a complete cure at Visit 10, will be invited to complete additional visits. Subjects that meet the extension criterion at Visit 10 will be evaluated again at Visit 11 (Week 60) to determine their eligibility to remain in the study until Visit 12 (Week 72).

Treatment efficacy will be evaluated on the basis of mycology (KOH test results and culture for dermatophytes) and clinical signs (investigator assessment of clear nail and length of unaffected nail as determined by planimetric photographic measurements). Persistence of treatment effect will be assessed during the post-treatment phase (Section 9).

Safety measurements will include local clinical signs and symptoms, including erythema, edema, hematoma, bruising, itching, and pain; and reports of adverse events (Section 10).

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6.2 Procedures and Assessments Flow

The major procedure and assessments performed by the investigator or delegated staff on the (target) great toenail during the study are summarized and sequenced in Table 6-2 for all visits categorized as either screening, treatment and post-treatment visits.

Table 6-2 Procedure and Assessment Flow

Procedure				Visits and Order of Procedure		
	Aim	Procedure / Tool	Subjects	Screen	Treatment	Post-Treatment
Target toenail assessment, nail clipping and notching						
	Standardized assessment of clear nail (growth) & treatment	Clipping and measurements of the nail with caliper / ruler; notching of the nail	All	1	1	1
Digital photography (Canfield Manual)						
	Visual evidence of disease and emergence of clear nail	Digital image capture of the target great toenail per Canfield Manual	All	2	2	2
Distal Digital Block						
	Local anesthesia of nail unit	Infiltration anesthesia (liocaine 2%)	All		3	
Subungual Sampling for Mycology						
	Laboratory confirmation DLSO	Subungual material sampling by curettage	All	3		3
Precannulation Procedure						
[redacted]						
HTS-519 Insert Administration Procedure						
[redacted]						
End of Assessment of Procedure(s) – Site Administration Reaction						
	Local tolerability assessment of procedural site	Site Administration Assessment Scale	All		6	
End of Assessment of Procedure(s) – Digital Photography (Canfield Manual)						
	Documentation of areas of diseased nail, emergence of clear nail and status pre- and post procedure	Outline diseased nail and obtain digital image of the dorsal surface of the great toenail per Canfield Manual	All	4	7	4

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7 STUDY INTERVENTION

7.1 Investigational Product Description

The HTS-519 (Hallux Terbinafine Subungual) Insert is a [redacted]

7.1.1 Acquisition

The HTS-519 Insert will be supplied by the sponsor, Hallux, Inc. [redacted]

7.1.2 Formulation, Packaging and Labelling

The HTS-519 Insert is supplied [redacted]. Each applicator is packaged in a sealed pouch for single use. A label with the following information will be affixed to each unit package:

[redacted]

7.1.3 Product Storage and Stability

The HTS-519 Insert should be stored at room temperature 59-86^{0}F / 15-30^{0}C.

7.2 Dosage, Preparation and Administration of Study Product

Placement of HTS-519 Inserts [redacted]

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[redacted]

Dose determination therefore starts with measuring the [redacted] involved nail [redacted]

[redacted]

[redacted]

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[redacted]

7.3 Modification of Study Product Administration

Small deviations [redacted] is anticipated and referred to as opportunistic placement.

Anatomical nail and disease characteristics necessitating a different insertion point (opportunistic placement) than determined from Table 7-2 could includ [redacted]

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The investigator may decide to administer fewer HTS-519 Inserts than determined by [redacted]

With clearing of the nail [redacted] the number of HTS-519 Inserts should be adjusted accordingly.

[redacted]

Any modification to the optimal [redacted] administration as described above must be documented in the CRF.

7.4 Treatment Accountability and Compliance Checks

It is the investigator/Institution's responsibility to establish a system for handling study treatments and products. This includes:

- Maintaining accurate records of receipt of all test articles by a responsible person, including dates of receipt.
- Providing treatment to subjects only as directed in the protocol. Reasons for departure from the expected dispensing regimen must be recorded.
- Storing all study treatments and supplies at site in a secure, restricted access area (eg, a locked room) under room temperature conditions and protected from light, moisture, and freezing as stated on the label.
- Reconciling delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed and the quantity and date of dispensing. This record is in addition to any drug accountability information recorded in the CRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist, and copies retained in the investigator Site File.

[redacted]

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7.6 Assessment of Clinician and/or Subject Compliance with Study Procedural Intervention

Study treatments are administered by the treating investigator at Day 1, Day 29, and Day 57. [redacted]

The presence of HTS-519 Inserts after placement will be confirmed visually if not obscured [redacted]

7.7 Prior and Concomitant Medications/Treatments

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. It is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the CRF.

Prohibited medications include:

- Concomitant use of systemic antimycotics during the study. Topical antifungal medicines will be permitted for subjects who develop symptomatic tinea pedis during the course of the study but contact with the large target toe must be avoided.
- Use of lotions, creams, liquids, or polish on the target great toenail or the skin immediately adjacent to the target great toenail during the study is prohibited.

7.8 Allocation to Treatment

Each subject who satisfies the criteria to participate in the study will be assigned a unique subject number. The subject numbers will be assigned sequentially in the order in which subjects are enrolled. The investigator will administer the required number of HTS-519 Inserts [redacted]

7.9 Treatment Blinding Code

This is an open label study in which investigator and subject are not blinded to treatment.

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8 STUDY VISIT SCHEDULE AND CONTACTS

Study visits are based on the number of days from the date of the study visit at Baseline (Day 1) and summarized in Table 1-1. During the treatment phase a window of ±3 days is allowed for the study visit based on the date of Baseline. For all other study visits, a window of ±7 days is allowed for each study visit based on the date of Baseline.

8.1 Screening (Visit 1)

The screening visit will occur within approximately 6 weeks of the Baseline visit. At Screening, the following procedures will be completed for each subject:

- Explain the particulars of the study to potential subjects.
- Obtain and document informed consent from potential subjects before performing any study-related procedures.
- Obtain demographic, medical history and concomitant medication information.
- Review inclusion/exclusion criteria for eligibility.
- Perform a physical examination and obtain vital signs needed to determine eligibility.
- Evaluate the involved great toenail(s) for anatomical (nail width) and disease characteristics as per [redacted] and complete the Investigator Global Assessment Scale ([redacted] to confirm eligibility.
- Collect subungual samples by curettage from each great toenail for which there is clinical suspicion of the presence of onychomycosis. Examine subungual samples using KOH microscopy. Confirm the presence of hyphae and ship unused subungual material to the central mycology laboratory for confirmatory fungal culture for dermatophytes ([redacted] and enroll the subject into the study. The tissue sample for screening mycology may be collected up to 8 weeks before the start of study therapy.
- Outline affected area of the great toenail(s) and obtain a digital photograph of the dorsal surface of the toenail(s) for analysis by Canfield Scientific as described in the Canfield manual.

8.2 Allocation and Treatment Visits

8.2.1 Enrolment / Baseline, Day 1, (Visit 2)

Results of fungal cultures, clinical laboratory assessments, and digital photography analysis will be reviewed by the Principal investigator in order to notify subjects of their eligibility to continue in the study. Subjects meeting eligibility criteria will return for their Baseline visit within approximately 6 weeks of Screening. At Baseline, the following procedures are to be completed:

- Review inclusion/exclusion criteria for eligibility.
- Document any changes to medical history, physical condition, concomitant medications according to the subject's response since the Screening visit.
- Evaluate the involved great toenail(s) for anatomical (nail width) and disease characteristics as per [redacted] and complete the Investigator Global Assessment Scale ([redacted] to confirm eligibility.
- Determine the location of the great toenail designated as the target toenail for the duration the study. If both great toenails have clinical and laboratory evidence of

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onychomycosis, the one with the greater involvement will be designated as the target nail for the primary efficacy evaluation. Both great toenails may be treated.
- Notch the target toenail 3 mm from the lunula as a baseline for nail growth measurement ([redacted]
- Obtain subject evaluation of pain before, during and after the infiltration anesthetic and cannulation procedure ([redacted]
- Administer study treatment as described in [redacted] and record site administration reactions [redacted] if any.
- Obtain a digital photograph of the dorsal surface of the toenail(s) for analysis by Canfield Scientific as described in the Canfield manual.
- Dispense subject 7-day diary.
- Schedule the next day follow-up phone contact and Day 29 visit.

8.2.2 Day 29 ±3 days, (Visit 3), and Day 57 ±3 days, (Visit 4)

At study visit 3, and visit 4, the following procedures will be performed:
- Document any changes to concomitant medications and occurrence of adverse events according to the subject's response since the last visit.
- Retrieve the subject 7-day diary and review for completeness.
- Administer study treatment as described in [redacted] and record site administration reactions ([redacted] if any.
- Obtain subject evaluation of pain before, during and after the infiltration anesthetic and cannulation procedure ([redacted]
- Obtain a digital photograph of the dorsal surface of the toenail(s) for analysis by Canfield Scientific as described in the Canfield manual.
- Dispense subject 7-day diary.
- Schedule the next day follow-up phone contact and the Day 57 and Day 85 Visit as appropriate for the visit.

8.3 Post-Treatment Visits

8.3.1 Intermediate Visits: Day 85 ±7 days, (Visit 5 – Week 12), 113 ±7 days, (Visit 6 – Week 16), and 141 ±7 days, (Visit 7 – Week 20)

At study Visits 5, 6, and 7, the following procedures will be completed:
- Document any changes to concomitant medications and occurrence of adverse events according to the subject's response since the last visit.
- Retrieve the subject 7-day diary and review for completeness (Visit 5 only).
- Evaluate the (target) great toenail for clear nail and extent of clear nail using the Investigator Global Assessment Scale as described in [redacted]
- Obtain a digital photograph of the dorsal surface of the toenail(s) for analysis by Canfield Scientific as described in the Canfield manual.
- Schedule the Day 113 and 141 Visits respectively.

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8.3.2 Intermediate Visits: Day 169 ±7 days (Visit 8 – Week 24) and Day 253 ±7 days (Visit 9 – Week 36)

At the study visit 8 and 9, the following procedures will be conducted:

- Document any changes to concomitant medications and occurrence of adverse events according to the subject's response since the last visit.
- Evaluate the (target) great toenail for clear nail and extent of clear nail using the investigator Global Assessment Scale as described in [redacted]
- Collect subungual samples by curettage from each treated great toenail and ship to the central mycology laboratory for confirmatory fungal culture for dermatophytes and KOH microscopy as described in [redacted].
- Obtain a digital photograph of the surface area of the target great toenail for analysis by Canfield Scientific as per the Canfield Manual.
- Schedule the Day 253 and 337 Visits respectively.

8.3.3 End of Study, Day 337 ±7 days (Visit 10 – Week 48)

When the subject returns for the End of Follow-up Visit, the following procedures will be completed:

- Document any changes to concomitant medications and occurrence of adverse events according to the subject's response since the last visit.
- Perform a physical examination, including vital signs. Collect subungual samples by curettage from each treated great toenail and ship to the central mycology laboratory for confirmatory fungal culture for dermatophytes and KOH microscopy as described in [redacted]
- Evaluate the (target) great toenail for clear nail and extent of clear nail using the investigator Global Assessment Scale as described in [redacted]
- Obtain a digital photograph of the surface area of the target great toenail for analysis by Canfield Scientific as per the Canfield Manual.
- Schedule the Day 420 Visit for those subjects that in the opinion of the investigator have the ability to reach a complete cure over the next 24 weeks based on clinical improvement observed during the entire study duration and mycological status, or have reached a complete cure at this Visit.

8.4 Post-Treatment Extension Visits

8.4.1 Study Extension Visit, Day 420 ±7 days (Visit 11 – Week 60)

For those subjects returning for the Study Extension Visit, the following procedures will be completed:

- Evaluate the (target) great toenail for clear nail and extent of clear nail using the investigator Global Assessment Scale as described in [redacted]
- Collect subungual samples by curettage from each treated great toenail and ship to the central mycology laboratory for fungal culture for dermatophytes and KOH microscopy as described in [redacted]
- Obtain a digital photograph of the surface area of the (target) great toenail for analysis by Canfield Scientific as per the Canfield Manual.
- Schedule the Day 504 Visit for subjects with a complete cure at this visit and for those subjects that in the opinion of the investigator have the ability to achieve a complete cure by Visit 12.

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8.4.2 Study Extension Visit, Day 504 ±7 days (Visit 12 – Week 72)

For those subjects returning for the Study Extension Visit, the following procedures will be completed:

- Evaluate the (target) great toenail for clear nail and extent of clear nail using the investigator Global Assessment Scale as described in [redacted]
- Collect subungual samples by curettage from each treated great toenail and ship to the central mycology laboratory for confirmatory fungal culture for dermatophytes and KOH microscopy as described in [redacted]
- Obtain a digital photograph of the surface area of the (target) great toenail for analysis by Canfield Scientific as per the Canfield Manual.

8.5 Withdrawal Visit

For any subject who withdraws from the study prior to Week 48, the End of Study (Visit 10) assessments should be performed and recorded to the extent possible and appropriate.

8.6 Unscheduled Visit

Although every effort will be made to see subjects at the per protocol visits unplanned visits may occur. These unscheduled visits may occur to perform additional assessments or procedures outside of the protocol specific visit calendar. These assessments could be related to the emergence of new clinical signs and symptoms or adverse events, lab results or questions the subject may have about the study or for any other clinical reason.

Unscheduled visits will be assigned the designation Visit “0”. The date of the visit and observations relevant to the study will be recorded in the CRF (eg, adverse events, change in medication) under “unscheduled visit”. If there are no specific observations to be captured the reason of the visit is recorded in the medical records only.

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9 EFFICACY ASSESSMENTS

9.1 Evaluation of the Target Toenail

The investigator will clinically establish the presence of DLSO of the great toenail as well as any clinical involvement of other toenails. Thickness of subungual hyperkeratosis will be measured in millimeters (one decimal point) from the top of the nail plate to the nail bed, using a caliper. Nail width will be recorded in millimeters [redacted]

The affected area of the nail [redacted] may be outlined by the investigator prior to target toenail evaluation and digital image collection to facilitate central image review.

The assessments listed in [redacted] determine subject eligibility and treatment efficacy and are conducted after clipping the nail to the distal groove (the transverse demarcation extending across the distal digit that divides the hyponychium from the volar epidermis). Subjects are therefore allowed to cut their toenails, but not beyond the target nail's distal groove so as not to interfere with the assessment of clear nail.

9.1.1 Investigator Global Assessment of Clear Nail

Evaluation of clear nail will be based upon that portion of surface area of the nail that is clear of signs of disease (ie, nail dystrophy, onycholysis or subungual hyperkeratosis) attributable to onychomycosis and active infection. The investigator will assess the involved great toenail for the extent of clear nail using the investigator Global Assessment (IGA) Scale. Missing nail is considered diseased nail.

Table 9-1 Investigator Global Assessment Scale

[redacted]

Note that a completely clear nail is not necessarily a "perfect nail" as the appearance of the nail may be affected by comorbid and pre-existing conditions unrelated to DLSO, such as longitudinal ridging, lamellar nail splitting, trachyonychia, brittle nails, and trauma, that will not respond to antifungal treatment.

9.1.2 Digital Photography

A high resolution digital photograph of the target nail is taken with specialized photographic equipment and computer hardware standardized for distance and lighting provided by Canfield Scientific (central imaging lab) to document visual evidence of nail disease, nail clearance or status post subungual sampling or HTS-519 Insert administration.

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Each subject will place the target foot in the toe stop that also functions as an internal scale included in all images to allow objective measurements of clear nail. The digital image will be captured before and after treatment administration as per the Canfield manual provided as a separate document. The image will be electronically uploaded instantaneously to Canfield Scientific for immediate assessment of quality.

9.1.3 Subungual Sampling for Mycology

As described in [redacted] the investigator collects subungual samples by curettage from each great toenail for which there is clinical suspicion of the presence of onychomycosis.

At Screening samples will be examined by the investigator using KOH microscopy to confirm the presence of septate hyphae, and remaining subungual material will be sent to the mycology laboratory for KOH visualization and confirmatory fungal culture for dermatophytes. After the Screening visits, the samples may be sent to the laboratory without the on-site KOH microscopy.

If at Screening the KOH microscopy exhibits septate hyphae, but the culture fails to grow dermatophytes the culture may be repeated. If 2 sequential cultures are negative, it is recommended that the nail not be included in the study and no further cultures are attempted.

Cultures grown from samples taken during the study will be stored at the central mycology laboratory for future susceptibility testing at the end of the study. Results will be reported separately from the final study report.

9.2 Evaluations Associated with the Insertion Procedure

9.2.1 Insertion Point

[redacted]

9.2.2 Insertion Depth

[redacted].

9.2.3 Investigator Insertion Rating

A 5-point Likert scale will be used for the investigator's assessment of ease of insertion. The scoring ranges from 1-5 with (1) = very easy, (2) = easy, (3) = difficult, (4) = very difficult and (5) = impossible to administer the HTS-519 Insert.

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10 SAFETY ASSESSMENTS

The safety of HTS-519, administered subungually, will be assessed by monitoring local tolerability at the administration site, adverse events, and evaluating data from physical examinations and vital signs measurements.

10.1 Local Tolerability

Before and after placement of HTS-519 Insert(s) and at each visit the investigator will examine the nail unit and surrounding tissue for adverse signs and symptoms. Immediately following the administration of an insert the event of bleeding will be evaluated specifically by the investigator using the following scale:

Within 1 hour of treatment the subject will record the level of . The signs and symptoms will be rated as 0 = none, 1 = mild, 2 = moderate, or 3 = severe as defined in

After each treatment the subject will be provided a 7-day diary to record the same assessments every evening using the rating scale described in detail in The day after treatment a phone contact will take place to ensure that the diary is completed and to collect any changes in medication and health status.

The presence or absence of a subungual hematoma will be documented by the investigator at every visit. In addition, over the course of the study, the investigator will observe the nail unit for signs of nail dystrophy, foreign body reactions, and infectious processes such as paronychia and osteomyelitis.

10.2 Patient Assessment of Pain

The numerical rating scale (NRS) is a one-dimensional pain intensity scale with a number 0 (no pain) located on the left and a number 10 (worst pain imaginable) displayed on the right of the horizontal scale.[27] The subject will be instructed to select a number that best represents their perception of the degree of pain. The magnitude of the pain associated with anesthesia, access to the subungual space and placement of a HTS-519 Insert is collected on paper by the subject and subsequently recorded in the CRF.

The subject will be provided a subject diary for seven days following each insertion procedure to record pain levels using the same numerical rating scale every evening.

10.3 Physical Examination and Vital Signs Measurements

An abbreviated physical examination will be performed at Screening and Week 48. The examination will focus on the essential aspects of the subjects' illness and general physical condition, including examination of the foot for the presence of tinea pedis and adequacy of circulation etc..

Vital signs assessed include heart rate and blood pressure using a blood pressure recording device with an appropriate cuff size. Measurements will be made after the

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subject has been resting supine for a minimum of 5 minutes. Weight will be measured as well.

10.4 Adverse Events

10.4.1 Adverse Event Definition and Documentation

An adverse event (AE) is any untoward medical occurrence in a subject, administered an investigational product and which does not necessarily have to have a causal relationship with this treatment (21 CFR 312.32). An AE (also referred to as an adverse experience) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

Adverse events may be volunteered spontaneously by the subject or discovered as a result of general, non-leading questioning, through physical examination, laboratory test, or other means.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must be recorded. Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if the signs or symptoms associated with the medical condition deteriorate at any time during the study, it should be recorded as an AE.

Abnormal laboratory values or test results will be recorded as AEs only if (1) they induce clinical signs or symptoms, (2) require therapy, or (3) are considered by the investigator to be of clinical significance. Prior medical conditions/diseases are considered AEs only if they worsen after the start of protocol-specified study procedures.

All AEs reported or observed from the time a subject signs informed consent until exit from the study must be recorded in detail on the appropriate page of the CRF and followed until the event is resolved, the event reaches a clinically stable outcome, or the subject is lost to follow-up. For each AE, the AE record will include type of event, start and stop dates, severity (mild, moderate, or severe), seriousness, relationship to the study treatment (definite, probably, possibly, unlikely, or not related), actions taken (required treatment or observations), and outcome.

Adverse events that are prospectively collected as outcomes or observations include procedure related pain, post-treatment symptoms collected in a subject diary and an investigator assessment of the nail before and after treatment. For the purpose of this study this prospectively collected information will not be again reported as AEs unless:

- Considered clinically significant by the Investigator,
- Requiring treatment or study treatment modification, or
- Meeting the criteria for a Serious Adverse Event (SAE)

A temporary change in nail appearance reasonably associated with healing or clearing of disease is not considered an adverse event, unless any of the 3 criteria above apply.

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10.4.2 Serious Adverse Events

An AE or SAR is considered “serious” (see 21 CFR 312.32) if, in the view of either the investigator or sponsor, the adverse event:

- Results in death.
- Is life threatening (i.e., the subject was 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).
- Requires insubject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct activities of normal life.
- Is a congenital anomaly / birth defect.
- Is considered to be an important medical event.

Based upon medical and scientific judgment, important medical events that may not be immediately life threatening, or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above may be considered a serious adverse event (SAE).

Hospitalizations are defined as official admission, not necessarily an overnight stay for observation or for an out-subject procedure. If, however, the investigator feels that the cause of the out-subject procedure or overnight stay is medically significant, then the event will be considered an SAE with the serious criteria of Important Medical Event. A hospitalization for social reasons in the absence of an AE is not an SAE. Additionally, if a subject is hospitalized for a procedure that was planned prior to the study, this will not be considered an SAE. If a hospitalization is prolonged, such as for a fever, then that fever will be considered an SAE.

10.5 Time Period and Frequency for Event Assessment and Follow-up

The investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation in the CRF. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

10.6 Adverse Event Characteristics

Each AE has three attributes as described in [redacted]. Severity and relationship to study treatment are recorded in the CRF by the investigator. The Medical Monitor and the Study PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

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10.6.1 Adverse Event Severity

The investigator will classify the severity (intensity) of each AE according to the following definitions summarized in Table 10-1:

Table 10-1 Adverse Event Severity

Classification	Definition
Mild	[redacted]
Moderate	
Severe	

It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

10.6.2 Adverse Event Relationship to Study Treatment

All events considered to be noxious and unintended responses to an investigational product related to any dose should be considered an Adverse Reaction (AR). The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

A suspected adverse reaction (SAR) therefore indicates any AE for which there is a reasonable possibility that the drug caused the adverse event, ie, there is evidence to suggest a causal relationship between the drug and the adverse event.

The determination of the causal relationship between the drug and the adverse event will be based in part on the investigator's assessment of the relationship of the AE to the investigational treatment. An AE considered by the investigator to be probably or definitely related to the study treatment is to be considered an AR, and an AE considered by the investigator to be possibly related to the study treatment is a SAR, but not an AR. An AE considered by the investigator unlikely to be related, or to be unrelated, to the study treatment, is not a SAR, unless the sponsor determines otherwise based on other evidence.

The investigator will assess the likely relationship of each AE to the investigational product according to the definitions outlined in Table 10-2.

Table 10-2 Terms for Defining Relationship of Adverse Events to Study Product

Association	Definition	Interpretation
Not Related	[redacted]	Adverse Event (AE) - Unrelated
Unlikely Related		

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Association	Definition	Interpretation
Possibly Related	[redacted]	Suspected Adverse Reaction (SAR) - Related
Probably Related		Adverse Reaction (AR) - Related
Definitely Related		

10.6.3 Expectedness of Adverse Events

An AE or SAR is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

"Unexpected" as used in this definition, also refers to AEs or SARs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

10.7 Reporting Procedures

Clinical safety personnel will be available for SAE reporting on a 24-hour basis. Reports will be reviewed during normal business hours. Investigator instructions and sponsor requirements for safety reporting are outlined in [redacted] respectively.

The Medical Monitor for this study is [redacted]

10.7.1 Investigator Reporting Requirements - SAE

Site personnel must report any AE that meets SAE criteria or unusual frequency of AEs within 24 hours from the time staff is aware of the event to the medical monitor (or designee for this study), even if the event(s) appear to be unrelated to study treatment.

Follow-up information about a previously reported SAE must also be reported to the medical monitor (or designee) within 24 hours of receiving it. Follow-up reports regarding the status of the SAE and the subject's subsequent course should be submitted until the SAE has subsided, the condition stabilized (in the case of persistent impairment), the subject receives alternative therapy, or the subject dies.

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Electronic submission of initial and follow-up information and automatic e-mail notification of the Medical Monitor will occur when the investigator completes the SAE report form in the CRF. Once submitted, the medical monitor or designee will send a confirmation email to the investigator within 1 business day. In the event a confirmation email is not received, contact the Medical Monitor directly by phone, email or fax. A confirmation of receipt will be sent within 1 business day.

If the SAE has not been previously documented (ie, is a new occurrence) and it is thought to be related to the investigational product (or therapy), the medical monitor may contact the investigator to obtain further information. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same product (or therapy) that this SAE has been reported.

The IRB should also be notified of SAEs and of any follow-up information in writing according to their reporting requirements.

10.7.2 Sponsor Reporting Requirements

Hallux must notify the FDA and all participating investigators of any potential serious risks associated with use of the study product as they are identified during this clinical trial. This notification must be made as soon as possible but in no case later than 15 calendar days (7 calendar days for fatal or life-threatening SARs) after determining that the information qualifies for reporting based on the following criteria:

10.7.2.1 Serious and unexpected suspected adverse reactions.

The sponsor must report any suspected adverse reaction that is both serious and unexpected to all concerned Investigators/Institutions, to the Institutional Review Boards (IRBs), where required, and to the regulatory authority(ies). A single or small number of events of a specific AE must be reported as a SAR only if there is a reasonable possibility that study product caused the event (ie, there is evidence to suggest a causal relationship between the study product and the AE). For example:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome and acute liver failure);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than a concurrent or historical control group.

10.7.2.2 Increased rate of serious suspected adverse reactions

The sponsor must also report any clinically important increase in the frequency of a serious SAR over that which is listed in the protocol or Investigator’s Brochure.

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10.7.2.3 Unexpected fatal or life-threatening suspected adverse reactions

The sponsor must notify the FDA of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

Expedited reports should comply with the applicable regulatory requirement(s) and with the International Conference on Harmonisation (ICH) Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A). The Sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

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11 STATISTICAL CONSIDERATIONS

A detailed and comprehensive Statistical Analysis Plan (SAP), describing all statistical analyses will be prepared and approved prior to database lock. The statistical analysis and report will conform to relevant ICH guidance. Any changes to the statistical methods need not be reported as a protocol amendment but must be documented in the clinical study report.

11.1 Statistical Hypotheses

[redacted]

11.2 Sample Size Determination

[redacted]

11.3 Final Analysis Plan

The standard summary statistics for analysis of the categorical baseline and outcome variables ([redacted]) will be count and proportion (expressed as percentage). The following standard summary statistics will be used for analysis of continuous baseline and outcome variables: N, mean, standard deviation, median, quartiles, and maximum and minimum.

11.3.1 Analysis Populations

[redacted]

11.3.2 Demographics and Baseline Characteristics

Subject demography and baseline characteristics will be presented in by-subject listings and summarized by descriptive statistics. A separate summary and listing will be provided for subjects discontinued before randomization (Screen Failures).

11.3.3 Prior and Concomitant Medications

Prior and concomitant medication information for all randomized subjects will be presented in a by-subject listing.

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11.3.4 Statistical Methods for Efficacy Parameters

The appropriate standard summary statistics will be used for all efficacy variables. [redacted]

11.3.5 Safety Analysis

Extent of exposure to study treatments will be summarized according to the number of subjects exposed and the total dose administered.

Incidence, relatedness, and severity of AEs and SAEs will be tabulated by preferred term and system organ class using the most recent version of MedDRA. Adverse events will be summarized by presenting the number and percentage of subjects having any AE, having an AE in each body system and having each individual AE.

Of particular interest are the AEs involving administration site reactions (ie erythema, burning/stinging, itching, scaling, swelling/edema) and self-reported pain. These will be listed separately and summarized by frequency counts at each visit and at each time point of the subject diary. In addition, the incidence of SAEs, drug related AEs, serious and drug-related AEs, and any AEs resulting in discontinuation from the study will be listed.

Vital signs measurements and physical examination findings, together with changes from baseline assessments, will be described using standard summary statistics.

Baseline for all physical examination evaluations and vital signs measurements will be defined as the last evaluation just prior to the first administration of study treatment.

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12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data may be written or typed by authorized and qualified study personnel directly from clinical observation, or they may be generated, on paper or electronically, by an automated measurement device or system of devices.

Source documents may include, for example, subject medical records, screening or enrollment logs, laboratory reports, electrocardiograms, subject diaries, drug dispensing and collection records, drug accounting logs, study notes, and study-related correspondence.

In order to ensure the integrity of the study data, procedures must be in place to allow every element of the study data to be traced to its source. It is the responsibility of the study monitor to verify that data recorded on the CRF are an accurate transcription of the source data. The source documents are typically the property of the study site itself, and may include data that are not relevant to the study database and are therefore not subject to study-related quality control procedures.

The study site must maintain a list of originators (persons, devices, and instruments) of all source data. The list for persons should include signatures, initials, and user identification (user ID) tags that will permit a reviewer to trace the source data records to their originator.

In order to facilitate source data verification of the CRF, all source documents must be maintained at the study site in individual subject folders. While not strictly a source document, the original signed Informed Consent document is to be kept in the same folder for ease of review. Source documents must be maintained in the same way for all enrolled study subjects and for screen failures (individuals who are screened for the study but who do not meet the entrance criteria).

The investigator must assure that the subject's anonymity will be maintained. On all study documentation, with the exception of the consent form and subject identification logs, subjects will only be identified by their unique identification code and initials and will not be referred to by name.

All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, U.S. Food and Drug Administration (FDA) or other regulatory agencies, or the IRB.

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13 QUALITY CONTROL AND QUALITY ASSURANCE

As specified in the investigator's agreement, the investigator agrees to allow the sponsor's (or designated CRO's) study monitor, quality assurance auditor, health authority inspector, and/or IRBs inspector direct access to all relevant source documents, and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues.

13.1 Monitoring Procedures

During the study, the study monitor will review the progress of the study on a regular basis to ensure adequate and accurate data collections. Specific data verification procedures will be described in a study-specific monitoring plan that includes aspects of ongoing remote and periodical on-site monitoring activities.

Monitoring site visits to review CRFs, subject case notes, administrative documentation including the investigator Site File, and telephone communications with site staff, will be performed throughout the study.

At each study monitoring visit, the investigator will make available all records pertaining to the study. To allow sufficient time to assemble documentation for the study monitor, monitoring visits will be confirmed in advance of planned visits.

Significant or relevant communications with the Sponsor or sponsor's designated study representative should be documented by the site and retained for the study file.

13.2 Quality Assurance

In addition to the routine monitoring procedures and to ensure compliance with GCP and all applicable regulatory requirements, the investigator(s)/Institution(s) will permit study-related audits, IRB review, and regulatory inspection(s), providing direct access to all source documents, drug records, and original CRFs at some or all of the study sites used in the study.

The sponsor or sponsor's representative, will provide prior notice of such a planned GCP audit, during or after completion of the study. The investigator should promptly notify the sponsor or CRO of any audits scheduled by any regulatory authorities or IRB and promptly forward copies of any audit reports received to the sponsor.

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14 ETHICS COMMITTEE REVIEW/INFORMED CONSENT

14.1 Ethical Conduct of the Study

The study will be conducted in accordance with ethical principles expressed in ICH E6(R1): Good Clinical Practice (GCP) guidelines, the WMA Declaration of Helsinki,[28] IRBs, and in accordance with the United States Title 21 Code of Federal Regulations (CFR) Part 50 Protection of Human Subjects.

This study must be carried out in compliance with the protocol, applicable laws and US regulatory requirements.

14.2 Institutional Review Board

The final study protocol, subject informed consent form and other documentation or information provided subjects will be reviewed and approved by the IRB in compliance with local regulations. Approval will be received in writing before initiation of the study.

Any changes to the study design will be formally documented in protocol amendments and approved by the IRB prior to implementation, except in the case of changes made to protect subject safety, which will be implemented immediately.

14.3 Informed Consent

The investigator is responsible for obtaining informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study medications are administered. The investigator or designee will answer any questions that may arise. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate.

This informed consent should be given by means of a standard written statement, provided in non-technical language. The subject is required to read and review the document or have the document read to him or her before signing and dating it. If written consent is not possible, oral consent can be obtained, if witnessed by a signed statement from one or more persons not involved in the study, mentioning why the subject was unable to sign the form. No subject can enter the study before informed consent has been obtained from him/her, or his/her legally authorized representative.

Subjects will also be asked to consent to allow the sponsor, sponsor representative, or external regulatory auditor to review their medical records to confirm compliance with GCP.

The acquisition of informed consent should be documented in the subject's clinical or research record and the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in the investigator Site File and a copy of the signed consent should be provided to the subject prior to participation in the trial.

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The subjects will be informed that they may withdraw from the study at any time without prejudice to further treatment. They will receive all information that is required by local regulations and ICH guidelines.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

Individuals of any gender or racial/ethnic group may participate in this study as long as their age is between 18-74 inclusive.

14.5 Disclosure and Confidentiality

14.5.1 Confidentiality of Study Documentation

By signing the protocol, the investigator agrees to keep all information provided by the sponsor in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by the study sponsor (ie, protocols, investigators' brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorization from the sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

14.5.2 Privacy of Individual Health Information

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to subjects.

While all data records will be identified by the corresponding subject number, the identity of the subject will be held in confidential source documents at the study site. No information concerning the study or the data will be released to any unauthorized third party except as specifically authorized by each individual subject in the written informed consent.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records. All study personnel with access to this information are legally bound not to disclose it.

14.6 Future Use of Stored Specimens and Other Identifiable Data

De-identified digital images of the subject’s toenail(s) will be stored during the duration of the study at Canfield Scientific, before being archived at the sponsor after study completion.

No biological samples will be stored for future use and no genetic testing will be performed.

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15 DATA HANDLING AND RECORD KEEPING

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

15.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

Once recorded, the study data must be protected from unauthorized modification or deletion, and all authorized modifications and deletions must be securely linked in the permanent record with their author, time of change, and reason for change (ie, the audit trail must be maintained). There must be a procedure whereby the PI certifies the data to be accurate and complete and releases the data for transmittal to the sponsor or CRO.

Procedures and specifications for management of the study data once released to sponsor or CRO will be described in detail in a separate Data Management Plan to be approved by the sponsor. This document will include definitions of the data sets and variables, references to prevailing SOPs, and descriptions of the following procedures:

- Procedures for data management review and query processing;
- Procedures for assignment and medical review of standard preferred-term coding of adverse events, concomitant medications, or other terminology collected in the study data;
- Procedures for electronic data transfer of study data elements from external non-CRF data sources, such as analytical, imaging, or other specialized laboratory services;
- Procedures for certification and closure of the database prior to unblinding.

Procedures for data collection and data management will be designed to ensure that each data element may be traced with a high level of confidence from its originator or recorder to its representation in the study database and then to its place in the analysis and integrated clinical study report according to GCP.

At each stage in the data collection and management process, the data must be accessible for review by authorized parties, such as the study monitor, a designated auditor, and an FDA inspector.

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15.2 Data Capture Methods

The primary data collection tool for the study is an electronic data capture (EDC) or CRF system designed to record all the data required by the protocol in designated labeled fields. A computer generated password and specific roles to access and use the EDC will be provided to study staff prior to study start.

Each page of the CRF is headed by identifying information including the study number, subject number, and study visit number or time point. Entries to the CRF are made by authorized site staff according to written CRF Completion Guidelines for the study or as instructed by a qualified trainer at study initiation.

Case report form entries may be written directly from clinical observation or they may be transcribed from source data recorded at an earlier time. The originator of the data (ie, the individual making the observation or evaluation) date and time of the recorded event are captured electronically.

Each CRF must be completed within 5 days of a visit, reviewed, and subsequently signed, and dated by the investigator as outlined in the project timeline. The completed CRF will be reviewed by data management after monitoring is complete. A copy of the completed CRF will be provided to the investigator. The copy will remain at the site in the investigator's files.

Computer systems and devices which are used to produce electronic source documents must conform to the principles described in relevant regulatory guidances (eg, the FDA's Draft Guidance [December 2010] on Electronic Source Documentation in Clinical Investigations, and references therein), which are designed to ensure the security and integrity of those data sources.

15.3 Types of Data

During the conduct of this study, safety and efficacy data will be collected in the CRF. Safety data consist of standard adverse event data as well as specific site administration reaction data. Efficacy data consist of investigator assessments of clear nail and laboratory data from the Center of Medical Mycology and emergence of clear nail. Outcome data include assessments of pain and ease of insertion.

15.4 Schedule and Content of Reports

The following reports will be generated during the conduct of this open label study to monitor study progress and quality.

A screening log will be kept to monitor and analyze reasons for screen failure.

The quality of subungual sampling will be assessed for the ability of the investigator to visualize septate hyphae. In addition, results from the Center of Medical Mycology will be reviewed for evidence of bacterial contamination of the sample and the ability of a clinical diagnosis of DLSO to be confirmed by laboratory means. The review may lead to modifications to the subungual sampling technique at the site.

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[redacted] digital image result reports issued for each subject at each visit, will be reviewed for photo quality, correct trimming of the nail, subungual sampling technique and congruence with sequential IGA results.

Early terminations will be tracked in order to ensure that subjects return for their final visit. Protocol deviations will be monitored and the determination of protocol deviations will be determined prior to unlocking the database.

15.5 Study Records Retention

The investigator is required to maintain all study documentation, including regulatory documents, copies of CRFs, signed informed consent forms, and records for the receipt and disposition of study medications, for a period of at least 2 years following the last approval date of a marketing application in an ICH region or until at least 2 years after the formal discontinuation of clinical development of the investigational product, whichever comes later.

15.6 Publication and Data Sharing Policy

Following completion of the study, the data may be considered for a formal presentation at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the investigator(s) to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

15.7 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation, intentional or unintentional, from the approved protocol that may affect the subject's rights, safety, or well being and/or the completeness, accuracy, and reliability of the study data.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Investigators will be notified of deviations in writing by the monitor and corrective action and preventative action plan will be instituted in accordance with sponsor's SOPs. The IRB will be notified of all protocol violations in a timely manner as per its guidelines.

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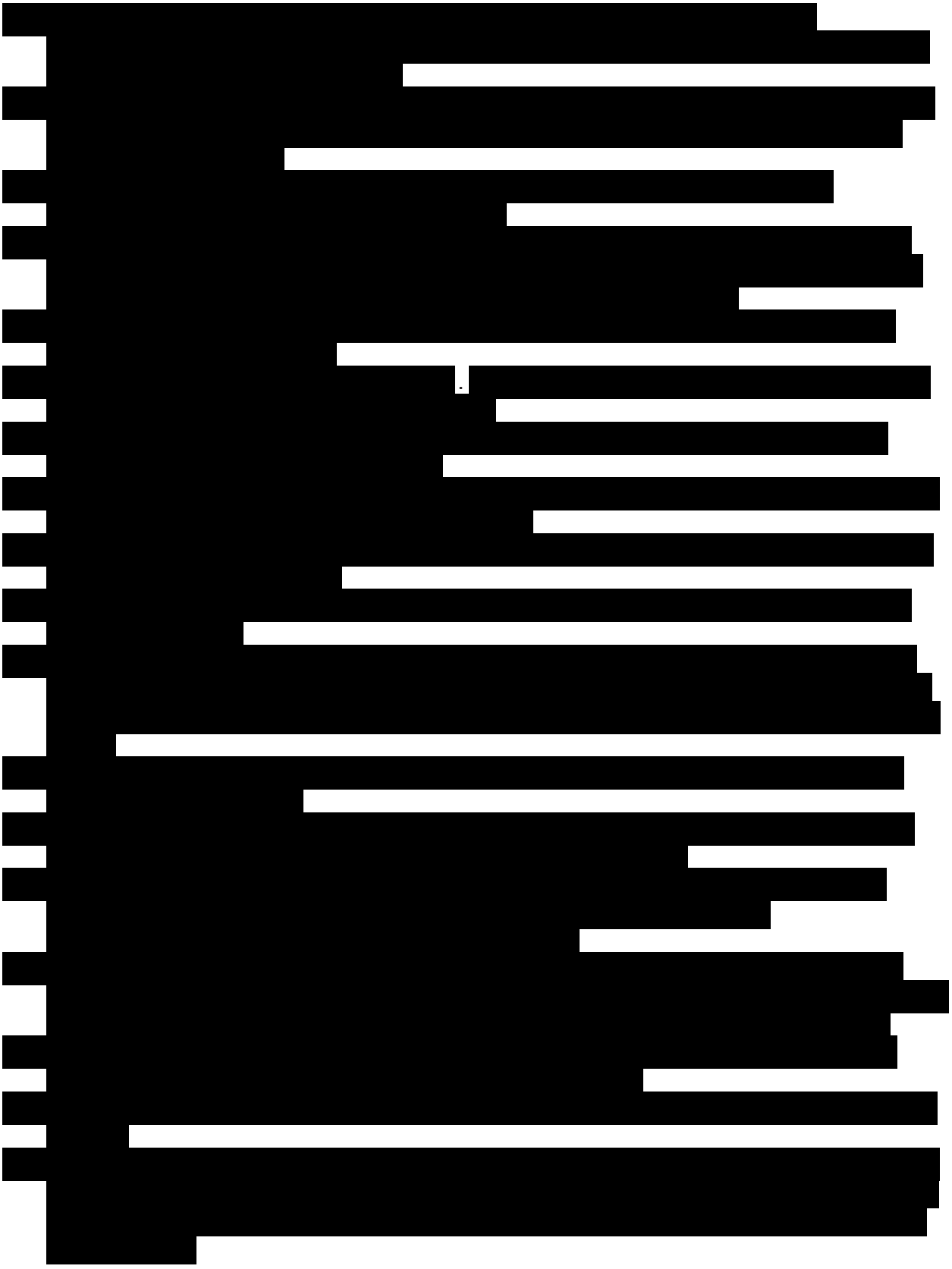
16 LITERATURE REFERENCES



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