

A Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Multi-Site Phase 2b Clinical Study to Assess the Efficacy, Safety and Tolerability of 8-Week Regimens of Novexatin[®], 10% Topical Solution (Taro Pharmaceuticals, USA, Inc.) in Patients with Mild to Moderate Onychomycosis

1.0 TITLE PAGE

Drug Products	Novexatin 10 % topical solution
Design	Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Multi-Site Phase 2b Clinical study
Population	Male or female patients, age 18 or over, with mild to moderate fungal infection of the toenail
Sponsor	Taro Pharmaceuticals USA, Inc
Protocol Number	NVXT 1404
Novum Study Number	71442603
IND #	111292
Protocol Date	July 08, 2016

NIIRB
July 19, 2016
APPROVED

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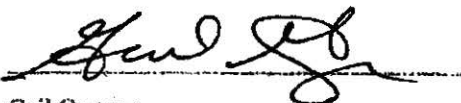
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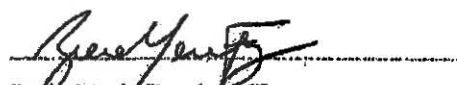
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SIGNATURE PAGE


We, the undersigned, have carefully read this protocol (# NVXT 1404, Rev 2) and agree that it contains all the necessary information required to conduct the study. The study will be performed according to this protocol, all applicable FDA regulations, ICH guidelines and Good Clinical Practice standards.


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Vice President Clinical Trials
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A Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Multi-Site Phase 2b Clinical Study to Assess the Efficacy, Safety and Tolerability of 8-Week Regimens of Novexatin[®], 10% Topical Solution (Taro Pharmaceuticals, USA, Inc.) in Patients with Mild to Moderate Onychomycosis

PRINCIPAL INVESTIGATOR'S SIGNATURE

I _____, agree to conduct the study (protocol # NVXT 1404, Rev 2) in accordance with FDA regulations, ICH guidelines and Good Clinical Practice. I understand that no deviations from the protocol may be made without the prior permission of the Sponsor (Taro Pharmaceuticals, USA, Inc.) or Novum Pharmaceutical Research Services, the company managing the study.

Principal Investigator

Date

A Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Multi-Site Phase 2b Clinical Study to Assess the Efficacy, Safety and Tolerability of 8-Week Regimens of Novexatin[®], 10% Topical Solution (Taro Pharmaceuticals, USA, Inc.) in Patients with Mild to Moderate Onychomycosis

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4.0 SYNOPSIS

Protocol Number	NVXT 1404 (Novum study # 71442603)
Title	A Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Multi-Site Phase 2b Clinical Study to Assess the Efficacy, Safety and Tolerability of 8-Week Regimens of Novexatin [®] 10% Topical Solution (Taro Pharmaceuticals, USA, Inc.) in Patients with Mild to Moderate Onychomycosis
Objectives	<ol style="list-style-type: none"> 1. Determine the rates of therapeutic cure of Novexatin[®] 10% topical solution (Taro Pharmaceuticals, USA) after daily dosing for one 8-week treatment period (Treatment Group A) and two 8-week treatment periods separated by a 32-week rest period (Treatment Group B), and Placebo (vehicle) topical solution (Taro Pharmaceuticals, USA) after two 8-week treatment periods separated by a 32-week rest period (Treatment Group C), at three test-of-cure visits (Day 141, Day 281 and Day 365) in patients with mild to moderate distal subungual onychomycosis of the target toenail. 2. Compare rates of therapeutic cure between Treatment Groups according to a hierarchical evaluation scheme detailed in the statistical sections. 3. Evaluate safety and tolerability of the two regimens of Novexatin[®] 10% topical solution (Treatment Groups A and B) in patients with mild to moderate distal subungual onychomycosis of the target toenail.
Sponsor	Taro Pharmaceuticals, USA, Inc.
Study Products	Test: Novexatin [®] 10% Topical Solution Placebo: Placebo (Vehicle) Topical Solution
Study Design	Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Multi-Site Phase 2b
Study Population	Up to 180 male or female patients, age 18 or over, with mild to moderate fungal infection of the toenail.

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Study Conduct	<p>Patients will be randomly assigned to the following treatment groups, with up to 60 patients per group</p> <p>Treatment Group A: Test treatment for Days 1 – 56 and Placebo treatment for Days 281 – 336</p> <p>Treatment Group B: Test treatment for Days 1 – 56 and Days 281 – 336</p> <p>Treatment Group C: Placebo treatment for Days 1 – 56 and Days 281 – 336</p> <p>Patients will be scheduled for a total of 7 clinic visits:</p> <ul style="list-style-type: none"> • Visit 1: Days -35 to -1 (Screening) • Visit 2: Day 1 (Baseline and Randomization / 1st Treatment start) • Visit 3: Day 57 ± 4 (1st Treatment completion) • Visit 4: Day 141 ± 7 (Interim) • Visit 5: Day 281 ± 14 (2nd Treatment start) • Visit 6: Day 337 ± 14 (2nd Treatment completion) • Visit 7: Day 365 ± 14 (4 weeks post-treatment) <p>Unscheduled visits will be allowed as deemed necessary by Investigator.</p>
Inclusion Criteria	<ol style="list-style-type: none"> 1. Male and female patients aged 18 or over. 2. Clinical diagnosis of onychomycosis of the target toenail (defined as one of the infected great toenails). 3. Onset of clinical signs of onychomycosis of the target toenail < 2 years of the screening. 4. Clinical signs and symptoms of onychomycosis, confirmed by positive KOH microscopy of the target toenail. 5. Before randomization, a confirmed positive fungal culture, of the target toenail. 6. Mild to moderate severity at Visit 1 as defined by Investigator's estimation of approximately 10% to 35% toenail involvement. 7. At least 5 mm of clear nail on the target toenail between the lunular proximal nail fold and the deepest extend of the onychomycosis. 8. The deepest extend of onychomycosis should not contact the lunula. 9. Besides onychomycosis, patients are in overall good health, or have a condition under stable treatment and are willing to comply with adequate foot care for the duration of the study. 10. Females of childbearing potential must not be pregnant or lactating at baseline (as confirmed by a negative urine pregnancy test with a sensitivity of less than 25 mIU/mL or equivalent units of human chorionic gonadotropin). Women of childbearing potential must agree to the use of a reliable method of contraception (e.g., total abstinence, IUD, a double-barrier method [such as condom plus

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	<p>diaphragm with spermicide], oral, transdermal, injected or implanted non- or hormonal contraceptive), throughout the study. If the female is using a hormonal contraceptive, the same product must be taken for 1 month before baseline and must agree not to replace with some other hormonal contraceptives during the study. A sterile sexual partner is not considered an adequate form of birth control.</p> <p>All females will be considered to be of childbearing potential unless they:</p> <ul style="list-style-type: none"> • Are post-menopausal, defined as women who have been amenorrheic for at least 12 consecutive months, without other known or suspected primary cause. • Have been sterilized surgically or who are otherwise proven sterile (i.e., total hysterectomy or bilateral oophorectomy) with surgery at least 4 weeks before baseline. Tubal ligation will not be considered a surgically sterile method. <p>Female patients of childbearing potential are defined as:</p> <ul style="list-style-type: none"> • Women without prior hysterectomy of at least 4 weeks, or who have had any evidence of menses in the past 12 months. • Females who have been amenorrheic for ≥ 12 months, but the amenorrhea is possibly from other causes, including prior chemotherapy, anti-estrogens or ovarian suppression. <p>11. Signed informed consent form which meets all current ICH/FDA regulations.</p>
Exclusion Criteria	<ol style="list-style-type: none"> 1. Patients under 18 years of age. 2. Females who are pregnant, lactating or likely to become pregnant during the study. 3. Patients with proximal onychomycosis, dermatophytomas, fungal spikes, limited lateral onychomycosis, white superficial onychomycosis or significant dystrophy of the target toenail that in the Investigator's opinion would impair the evaluation of onychomycosis. 4. Patient has total dystrophic or proximal subungal onychomycosis of the target toenail. 5. History or current diabetes and/or peripheral vascular disease. 6. Presence of mycotic spikes or patient has exclusively lateral groove involvement of the target toenail. 7. Patients with distal nail plate thickness of the target toenail greater than 3 mm. 8. Patient had no new nail growth requiring nail trimming in the target toenail over the previous 2 months. 9. Previous treatment for onychomycosis of the toenail within the last

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	<p>12 months that was unresponsive to treatment.</p> <ol style="list-style-type: none"> 10. Onychomycosis not caused by a dermatophyte (e.g., mold infection, <i>Candida spp</i> or bacterial infection). 11. Patients with a history of a trauma involving nail bed of the target toenail before onset of clinical signs of onychomycosis. 12. Patients with any significant active or past medical condition or abnormal laboratory value or who are required to start a medical therapy that in the opinion of the Investigator would make them unsuitable for study participation or compromise patient safety. 13. Patients who are unable to reach their infected toenails and administer the study product to affected toes. 14. Patients who are likely to apply toenail polish, cosmetic products or undergo professional pedicures during the study. 15. Current or history of psoriasis or Lichen planus within the previous 12 months. 16. Immunocompromised either because of concomitant disease (e.g., HIV), or ongoing treatment (e.g., chemotherapy), including patients with a history of organ transplant and patients on long-term corticosteroid therapy (refer to paragraph 9.3.3 for use of concomitant corticosteroid therapy). 17. Receipt of any drug as part of a research study within 30 days prior to dosing. 18. Use within 4 weeks before baseline of 1) topical antifungal therapies on the feet, 2) immunomodulators or 3) systemic corticosteroids. 19. Use of topical corticosteroids on the feet within 2 weeks before baseline. 20. Use of systemic antifungal agents for the treatment of onychomycosis or any antifungal with known activity against dermatophytes within the previous 24 weeks. 21. Current evidence of drug abuse or history of drug abuse within 1 year before the first dose, including, in the opinion of the Investigator, history of alcohol abuse or active alcoholism. 22. Inability to understand the protocol requirements, instructions, and study-related restrictions, the nature, scope, and possible consequences of the clinical study. 23. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions, such as uncooperative attitude, inability to return for follow-up visits, and improbability of completing the clinical study. 24. Patient is the Investigator or his/her deputies, research assistant, pharmacist, clinical study coordinator, other staff or relative thereof
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	<p>directly involved in the conduct of the clinical study or employed by the clinical site, or a first-degree relative of a site employee.</p> <p>25. Patients with previous exposure to the study drug, or with known allergy to the drug or any of its components.</p>
Route of Administration	Topical
Treatment	<p>Thin coat of study product will be applied to all toenails on feet with affected toenails once daily for either one or two 8-week intervals over an approximate 11-month intermittent treatment period (at Days 1 – 56 and Days 281 – 336) and 12-month study duration.</p> <p>The product should be applied at approximately the same time every day, preferably in the morning, after the patient has washed all toes with a non-medicated cleanser, rinsed with warm water, and patted dry with soft towel. The nails should be completely dry before applying the study treatment.</p>
Efficacy Endpoints	<p>The primary endpoint is the proportion of patients in each treatment group with a <u>complete therapeutic cure</u> of onychomycosis of the target toenail assessed at each of the two test-of-cure visits (Day 141 and Day 365).</p> <p>The secondary endpoint-1 is the proportion of patients in each treatment group with a <u>complete or almost complete therapeutic cure</u> of onychomycosis of the target toenail assessed at each of the two test-of-cure visits (Day 141 and Day 365).</p> <p>The secondary endpoint-2 is the proportion of patients in each treatment group with a <u>mycological cure</u> of the target toenail assessed at each of the two test-of-cure visits (Day 141 and Day 365).</p> <p>The secondary endpoint-3 is the proportion of patients in each treatment group with a <u>complete clinical cure</u> of the target toenail assessed at each of three test-of-cure visits (Day 141, Day 281 and Day 365).</p> <p>The secondary endpoint-4 is the proportion of patients in each treatment group with a <u>satisfactory clinical cure</u> of the target toenail assessed at each of three test-of-cure visits (Day 141, Day 281 and Day 365).</p> <p><u>Complete therapeutic cure</u> is defined as both complete clinical and mycological cure of the target toenail</p> <p><u>Almost complete therapeutic cure</u> is defined as both mycological and satisfactory clinical cure of the target toenail</p> <p><u>Mycological cure</u> is defined as a negative KOH test and a negative fungal culture.</p> <p><u>Complete clinical cure</u> is defined as 0% nail involvement.</p> <p><u>Satisfactory clinical cure</u> is defined as $\leq 5\%$ of the target toenail involvement.</p>

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Safety Endpoints	<p>Adverse events will be classified using standard MedDRA terminology Version 19 or higher and summarized by treatment group. Adverse events reported during the study will be tabulated in a summary table listing the type, date of onset, date of resolution, incidence, severity, outcome, action taken, and Investigator's opinion of relationship to the study product. Signs and symptoms of onychomycosis will not be considered adverse events, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers that it is in the patient's best interest to be dropped from continued participation in the study and given alternative therapy for their onychomycosis.</p> <p>If sufficient data exist, adverse event frequencies will be compared between treatments using Fisher's exact test or a similar test.</p> <p>Concomitant medication use during the study will be tabulated by patient.</p>
Sample Size Determination	<p>The primary statistical analysis of interest is a comparison of the rates (proportion of patients) of Complete Therapeutic Cure of Novexatin[®] 10% topical solution to the rate of Complete Therapeutic Cure of placebo in the Intent-to-Treat Population (ITT). The rates of Complete Therapeutic Cure for the Novexatin[®] 10% topical solution 8-week treatment regimens are expected to be approximately 49%. The rate of Complete Therapeutic Cure for placebo is expected to be approximately 21%. Approximately 46 patients in each treatment group in the ITT population will provide at least 80% power to show a difference at $p < 0.05$ (two-sided Z test and a pooled response rate for the standard error of the difference in proportions) between each of the active treatment groups and the placebo group. To allow for a 23% drop-out rate, a total of 180 patients will be enrolled in the study, with up to 60 patients in each of the treatment groups.</p>
Statistical Analyses	<p><u>Safety</u>: All safety parameters will be listed and summarized descriptively. Changes from baseline will be calculated, if appropriate.</p> <p><u>Efficacy</u>: In order to preserve an overall type-I error (alpha) of 5%, a hierarchical evaluation scheme for evaluation of complete and almost complete therapeutic cure, complete and satisfactory clinical cure and mycologic cure will be employed for the primary and secondary endpoints. The four comparisons of interest for the primary endpoint and the secondary endpoints -1 and -2 are:</p> <ol style="list-style-type: none"> 1. Group B versus Group C – at the test-of-cure visit at Day 365 2. Group A versus Group C – at the test-of-cure visit at Day 365 3. Group B versus Group A – at the test-of-cure visit at Day 365 4. (Group A + Group B) versus Group C – at the test-of-cure visit at Day 141

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	<p>The five comparisons of interest for the secondary endpoints -3 and -4 are:</p> <ol style="list-style-type: none"> 1. Group B versus Group C – at the test-of-cure visit at Day 365 2. Group A versus Group C – at the test-of-cure visit at Day 365 3. Group B versus Group A – at the test-of-cure visit at Day 365 4. (Group A + Group B) versus Group C – at the test-of-cure visit at Day 281 5. (Group A + Group B) versus Group C – at the test-of-cure visit at Day 141 <p>Statistical testing will begin with comparison 1. If statistical significance is attained with comparison 1 ($p < 0.05$), then a claim of superiority for comparison 1 can be made and the next comparison in the hierarchical evaluation scheme can be tested for statistical significance. If statistical significance is not attained for comparison 1 ($p \geq 0.05$), then testing of all subsequent comparisons is stopped. The hierarchical, conditional-stepwise evaluation scheme allows for each comparison to be evaluated at the 5% level, while preserving an overall type I error rate of no more than 5%. For the proportion of patients in each treatment group with a therapeutic, clinical or mycological cure of onychomycosis in the treatment area, the statistical analysis for superiority will be conducted using two-sided Z-Tests and a pooled response rate for the standard error of the difference in proportions for each comparison of interest. The primary and secondary analyses will be performed using an observed case (OC) analysis in the Intent-to-Treat (ITT) population. Patients discontinued because of lack of treatment effect will be included in the primary analysis as treatment failures.</p> <p>The following two sensitivity analyses will also be performed on the primary efficacy endpoints in the hierarchical, conditional-stepwise evaluation scheme:</p> <ol style="list-style-type: none"> 1. Analysis will be performed also including patients without an assessment at Day 365 \pm 14. Patients with missing data at Day 365 \pm 14 will be considered therapeutic failures. 2. Analysis will be performed also including patients without an assessment at Day 365 \pm 14. Patients in Group C with missing data at Day 365 \pm 14 will be treated as therapeutic successes and patients from the Groups A and B with missing data at Day 365 \pm 14 will be treated as therapeutic failures. <p>Similar sensitivity analyses on the primary endpoint will be conducted including patients without an assessment at Day 141 \pm 7 for the 4th comparison in the hierarchical, conditional-stepwise evaluation scheme. Efficacy results will be used to calculate the sample size for the Phase 3 studies.</p>
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5.0 SCHEMATIC

PROCEDURE	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening	Randomization / Baseline / 1 st treatment start	1 st treatment Completion	Interim Test of cure	2 nd treatment start Test of cure	2 nd treatment completion	4 weeks post – treatment Test of cure or ET
Day	-35 to -1	1	57 ± 4 (Week 8)	141 ± 7 (Week 20)	281 ± 14 (Week 40)	337 ± 14 (Week 48)	365 ± 14 (Week 52)
Informed Consent	X						
Inclusion/ Exclusion Criteria Review	X	X					
Demographics	X						
Medical History	X						
Physical Examination	X						X
Vital Signs	X		X		X	X	X
KOH test	X			X			X
Fungal Culture collection	X			X			X
Clinical Lab Tests	X		X				X
Target Nail trimming (if needed) before nail involvement/appearance assessments		X	X	X	X	X	X
Target toenail involvement (assessed by visual assessment)*	X	X	X	X	X	X	X
Planimetry Assessment		X	X	X	X	X	X
Evaluation of toenail condition/appearance (by patient and investigator)		X	X	X	X	X	X
Investigator Clinical Assessment	X	X	X	X	X	X	X
Urine Pregnancy Test**	X	X	X	X	X	X	X
Dispense study product, supplies		X			X		
Dispense Diary/Instructions		X	X	X	X	X	
Application site reactions			X	X	X	X	X
Collect unused/empty bottle			X			X	
Collect and Review Patient Diary			X	X	X	X	X
Adverse Event Assessments		X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X
Schedule next visit	X	X	X	X	X	X	

* At Visit 1, both toenails will be assessed if a bilateral infection of the big toenails are present.

** All women of childbearing potential

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6.0 LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Term
ADR	Adverse Drug Reaction
AE	Adverse Event
C	Celsius
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common toxicity criteria for Adverse Events
eCTD	electronic Common Technical Document
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
FU	Follow Up
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
kg	kilograms
KOH	Potassium hydroxide
LLOQ	Lower Limit of Quantitation
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
ml	milliliter
µl	microliter
NOAEL	No Observed Adverse Effect Level
NDA	New Drug Application
OHRP	Office of Human Rights Protection
OTC	Over-the-Counter
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
USA	United States of America
USP	United States Pharmacopeia
w/v	Weight per volume

7.0 BACKGROUND INFORMATION

7.1 Investigational product

10% Novexatin

Chemical name: Cyclo[arginyl-arginyl-arginyl-arginyl- arginyl-arginyl-arginyl], acetate

Chemical formula: C₄₂H₈₄N₂₈O₇

7.2 Background

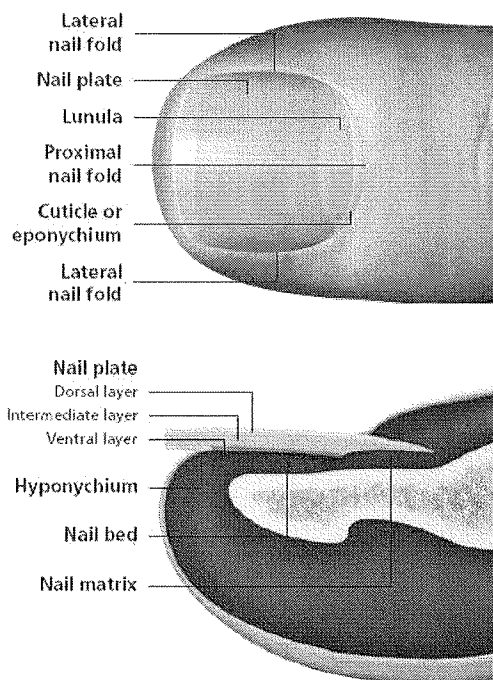
Onychomycosis (tinea unguium) is a fungal infection of the toenails that is predominantly caused by dermatophytic fungi. The most common clinical pattern of onychomycosis is distal subungual onychomycosis (DSO), in which the distal edges of the nail plate are the initial site of invasion by the causative fungi beginning at the hyponychium. The infecting organism migrates proximally through the underlying nail matrix. Mild inflammation develops resulting in focal parakeratosis and subungual hyperkeratosis.^{1,2} The nail becomes thick and opaque in color. Additionally, the nail can also become rough and crumbly. Almost all species of dermatophytes have been associated with onychomycosis, but the major dermatophytes associated with this condition (worldwide) are *Trichophyton rubrum*, and *T. mentagrophytes*. Other dermatophytes less commonly linked to onychomycosis are *T. tonsurans*, *T. violaceum*, *Epidermophyton floccosum*, *T. schoenleinii*, *T. concentricum*, and, rarely, *Microsporum gypseum*, *M. canis*, *M. audouinii*, *T. soudanense*, and *T. gourvilii*.

Population surveys have confirmed that such fungal infections of the nail affect more than 10% of the population in developed countries,¹⁻³ and more than 50% in some sub-populations.⁴ The incidence of onychomycosis has been increasing, owing to such factors as diabetes, immunosuppression and increasing age.¹ In the Amazon region, the dermatophytoses have the highest incidence among the superficial mycotic infections. This is attributable to environmental factors characteristic of this region, such as the high temperature and relative humidity, which provide conditions favorable to fungal dispersion and development.⁵ Onychomycosis can cause pain, discomfort and disfigurement and may produce serious physical and occupational limitations, as well as reducing quality of life.

Treatment of fungal toenail infection requires an understanding of the ultrastructure of the nail. Keratinocytes exist within the nail plate and are strongly linked by numerous desmosomes and phospholipid layers. The nail plate consists of 3 different layers: a thin ventral plate, a thick intermediate plate, and a thin dorsal plate (Figure 1). The cells of the dorsal plate are very flat and lack nuclei. The cells of the intermediate plate are less flat and have cytoplasmic portions. The ventral plate consists of 1-2 cell layers with nuclear residues. As a result of their composition and structure, the 3 nail plate layers can have different penetration characteristics for a medicinal product.

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Figure 1: Anatomy of the Nail



At present, the currently approved, marketed medicinal products available for the treatment of fungal nail infection have a number of shortcomings in regard to both safety and efficacy.^{2,6-8} The topical therapies (ciclopirox and amorolfine) have poor levels of efficacy.⁹ The systemic treatment options (terbinafine and itraconazole especially) have associated adverse effects and toxicity profiles of concern.^{10,11} Several authors reported liver toxicity and therefore monitoring of liver function during itraconazole therapy is important.¹¹ This unmet clinical need and a detailed understanding of host-pathogen interactions and the microbiology of fungal toenail infection have led to the development of Novexatin[®] by NovaBiotics. Novexatin is a backbone cyclized peptide of 7 L-isomer arginine residues; the chemical name is cyclo[arginyl- arginyl - arginyl - arginyl - arginyl - arginyl - arginyl], acetate. The L-isomer component comprises 93% of the Cyclo[7xArg] material with 7% as a single amino acid in the D-configuration.¹² This third-generation, cationic antimicrobial peptide (cAMP) provides the active component of a treatment for topical administration for fungal infection of the nail. Novexatin has the potential to address the significant efficacy and safety shortcomings of the limited number of current and emerging treatment options of onychomycosis.

7.3 Summary of Novexatin Non-Clinical Studies

From *in vitro* antifungal susceptibility studies novexatin exhibited dose-dependent fungicidal activity (median MIC₉₀ of 1 mM) and killed *Trichopyton* spp. via membranolysis within 3 hours of exposure in infected nail fragments.¹³ Treatment with Novexatin 10% for 28 days

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cleared quantifiable fungi in infected nail fragments and eradicated fungal growth in an *ex vivo* full thickness human toenail model.¹³

Single and repeated-dose toxicology studies by the intravenous, oral and dermal routes of administration have been performed with novexatin.¹⁴ No signs of local or systemic toxicity were seen in minipigs during repeated-dose dermal toxicology studies with up to 50 mg/kg/day of novexatin (> 10X proposed clinical dose) topically applied in the proposed clinical formulation. The dermal no-observed-adverse-effect level (NOAEL) was 50 mg/kg/day.¹⁴ Acute toxicity studies with intravenous doses of novexatin in rats and dogs identified the maximum tolerated dose (MTD) to be 2 mg/kg/day with the no observed adverse effect level (NOAEL) of 0.5 mg/kg/day in male rats and 1.25 mg/kg/day in female rats.¹⁴ In rats, toxicological signs seen at higher doses included transient signs such as abnormal respiration, subdued behavior, hunched posture, body held low, and rolling gait. Histopathology examination identified signs of kidney tubule regeneration in some animals dosed above the NOAEL. In a mouse study to investigate the potential oral toxicity mediated by a single dose of novexatin in the proposed clinical formulation an MTD of approximately 260 mg/kg was identified.¹⁴ The toxicological profile of the D- and L-enantiomers is equivalent and their bioactivity is identical.¹²

Toxicokinetic evaluations in the repeat studies showed no quantifiable plasma concentrations of novexatin in the minipig dermal administration study.^{12,14} Plasma data from the intravenous rat repeated-dose study showed a terminal plasma half-life ($t_{1/2}$) of approximately 3-6 hours.^{12,14}

An *ex vivo* study showed an average 3.53% of the radiolabelled novexatin applied to the surface of the nail was able to penetrate deep into the nail plate of uncompromised (i.e., by infection) intact full- thickness human nail.

In a human skin penetration study, novexatin absorption was minimal, accounting for 0.01% of the applied dose.¹² This low systemic exposure was also observed in dermal sensitization studies where the systemic exposure was below the lower limit of quantification (LLOQ) of the bioanalytical assay employed to monitor serum levels. Owing to the minimal systemic exposure seen from *in vitro* and *in vivo* dermal studies, major organ systems are not expected to be exposed to measureable levels of novexatin.

Details of the results of the non-clinical studies are provided in the Novexatin Investigator's Brochure.¹²

In a 60-Day Dermal (Semi-Occluded) Toxicity Study in the Minipig with a 14-Day Treatment-Free Period novexatin in a new formulation, administered by dermal application daily to the back for at least 60 consecutive days to the minipig, at concentrations of 5 % and 10 % was well tolerated. There was no evidence of either local or systemic target organ toxicity after the treatment period.

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7.4 Summary of Novexatin Clinical Studies

In Phase I/IIa studies with topical administration of Novexatin (referred to as a 9.3% solution representing 93 mg/mL of the L-configuration, equivalent to the current 10% solution) in 40 otherwise healthy patients with mild-moderate fungal infection of the toenail(s) on no current topical or systemic antifungal therapy showed a low incidence of adverse events (AEs).¹² AEs judged possibly related to study product were limited to application site reaction and headache. For AEs overall and for the events judged possibly related, the incidences among Novexatin- and placebo-treated patients were similar. Plasma concentrations of novexatin were below the lower limit of quantitation of the enzyme-linked immunosorbent assay (ELISA).¹²

In a Phase I study the systemic exposure and pharmacokinetics of novexatin in a new formulation was determined after repeated once-daily topical application of Novexatin solution, 10% in a maximal-use setting in adult patients with distal subungual onychomycosis of the toenails and in healthy adult subjects without onychomycosis. Safety was assessed through the evaluation of changes from pre-dose in physical examination findings, vital signs, clinical laboratory findings, 12-lead ECGs and by the occurrence of adverse events (type, frequency, severity) and premature discontinuations from study.

The results of this *An Open-Label, Multiple-Dose, Safety and Pharmacokinetic Study of Novexatin[®] Solution, 10% in Healthy Adult Volunteers and in Patients with Severe Distal Subungual Onychomycosis* study demonstrate that Novexatin solution 10% is safe and plasma concentrations of novexatin were below the lower limit of quantitation of the enzyme-linked immunosorbent assay (ELISA) following 28-day maximum-use once-daily topical doses in healthy subjects and patients with severe DSO.

No serious AEs were reported during the conduct of this study. The study product was well tolerated by all subjects. There were no screening or post-study laboratory results outside of normal range that were deemed Clinically Significant by the Investigator. All vital signs measurements were within normal range, returned to normal after repeated measurements, or were deemed Not Clinically Significant by the Investigator, except for subject 072, who had unrelated hypertension and began therapy after following up with primary care physician. There were no episodes of application site reactions. There were no AEs possible or probable related to the study product.

The Phase IIa pilot multiple-dose study determined the safety, tolerability and efficacy of Novexatin in a new formulation in patients with mild-to-moderate fungal infection of the toenail.

8.0 STUDY OBJECTIVES

1. Determine the rates of complete therapeutic cure of Novexatin[®] 10% topical solution (Taro Pharmaceuticals, USA) after daily dosing for one 8-week treatment period (Treatment Group A) and two 8-week treatment periods separated by a 32-week rest period (Treatment Group

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B), and Placebo (vehicle) topical solution (Taro Pharmaceuticals, USA) after two 8-week treatment periods separated by a 32-week rest period (Treatment Group C), at three test-of-cure visits conducted at Day 141, Day 281 and Day 365 in patients with mild to moderate distal subungual onychomycosis of the target toenail.

2. Compare rates of complete therapeutic cure between Treatment Groups according to a hierarchical evaluation scheme detailed in the statistical sections.
3. Evaluate safety and tolerability of the two regimens of Novexatin[®] 10% topical solution (Treatment Groups A and B) in patients with mild to moderate distal subungual onychomycosis of the target toenail.

9.0 INVESTIGATIONAL PLAN

9.1 Study Design and Plan Description

This randomized, placebo-controlled, double-blind, parallel-group, multi-site study is designed to evaluate and compare the efficacy and safety of two dosing regimens of Novexatin[®] 10% topical solution (Taro Pharmaceuticals USA) for the treatment of mild to moderate distal subungual onychomycosis of the target toenail. Additionally the active formulation in these regimens will be assessed for superiority to a placebo topical solution.

Up to 180 eligible patients with distal subungual onychomycosis who meet all the inclusion criteria and none of the exclusion criteria will be enrolled into the study at Visit 1. Patients must be at least 18 years of age, in overall good health. They should have a current diagnosis of distal subungual onychomycosis of mild-moderate severity. Before any study-specific procedures are performed all patients will read and sign the IRB-approved informed consent form.

At least 60 qualified patients in each treatment group will receive randomized and blinded study product. The randomization scheme will be 1:1:1 (Active Treatment A: Active Treatment B: Placebo C). The study products are:

Test: Novexatin[®] 10% Topical Solution (Taro Pharmaceuticals, USA)

Placebo: Placebo (Vehicle) Topical Solution (Taro Pharmaceuticals, USA)

Patients will be assigned to one of the three treatment groups as outlined below and described in Section 9.4 of this protocol.

Treatment Group A: Test treatment for Days 1 – 56 and Placebo treatment for Days 281 – 336

Treatment Group B: Test treatment for Days 1 – 56 and Days 281 – 336

Treatment Group C: Placebo treatment for Days 1 – 56 and Days 281 – 336

Treatment and study durations will be as follows:

Study Duration: 365 days (52 weeks)

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Patients will undergo evaluation for clinical and mycological cure of onychomycosis at each of the 7 clinic visits. Randomized patients who withdraw from the study will not be replaced. The study will be conducted according to the following schedule:

Visit Schedule:

- **Visit 1:** Days -35 to -1 (Screening)
- **Visit 2:** Day 1 (Baseline and Randomization / 1st Treatment start)
- **Visit 3:** Day 57 ± 4 (1st Treatment completion)
- **Visit 4:** Day 141 ± 7 (Interim)
- **Visit 5:** Day 281 ± 14 (2nd Treatment start)
- **Visit 6:** Day 337 ± 14 (2nd Treatment completion)
- **Visit 7:** Day 365 ± 14 (4 weeks post – treatment)

The primary efficacy endpoint is the proportion of patients in each treatment group with a complete therapeutic cure of onychomycosis of the target toenail assessed at Day 141 and at the last test-of-cure visit at Day 365 following either one 8-week treatment period or two 8-week treatment periods. The safety profile of each treatment group will be evaluated by comparing adverse events, application site reactions, monitoring vital signs and changes in clinical laboratory results obtained throughout the study.

The definitions of efficacy variables are stated below:

- **Complete Therapeutic cure:** Complete Clinical Cure and Mycological Cure
- **Complete Clinical Cure:** A patient with 0% nail involvement
- **Mycological Cure:** Negative KOH and negative culture for dermatophytes associated with onychomycosis
- **Satisfactory Clinical Cure:** ≤ 5% of the target toenail involvement

9.2 Selection of Study Design

Study product dosing is based on previous clinical studies with Novexatin and doses recommended in Investigator's Brochure. As the product composition (cationic peptide) is not comparable to currently marketed products, the study will be conducted in accordance with FDA advice and further communication regarding this class of drugs, specific recommendations for IND 111292, and input from Taro Pharmaceuticals, USA.

9.3 Selection of Study Population

The study will include patients who are diagnosed with onychomycosis by clinical and also microbiological analysis of samples taken from the toenail. In order to participate in this study, patients must have positive cultures.

The stage of 'mild-moderate' will describe the degree of fungal infection of the toenail, and this will be determined by examination of the appearance of the affected toenail(s). Patients with involvement of more than a single toenail will have evaluation based on both big toenails if a

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bilateral infection is present at screening. At Visit 2, a target toenail will be identified by the investigator and all further evaluations will be based on the target toenail. See Appendix A for target toenail identification.

Patients with concurrent disorders that would increase the risk of study participation or confound the interpretation of results, in the judgment of the Investigator, will not be included in the clinical study.

9.3.1 Inclusion Criteria

1. Male and female patients aged 18 or over.
2. Clinical diagnosis of onychomycosis of the target toenail (defined as one of the infected great toenails).
3. Onset of clinical signs of onychomycosis of the target toenail < 2 years of the screening.
4. Clinical signs and symptoms of onychomycosis, confirmed by positive KOH microscopy of the target toenail.
5. Prior to randomization, a confirmed positive fungal culture, of the target toenail.
6. Mild to moderate severity at Visit 1 as defined by Investigator's estimation of approximately 10% to 35% toenail involvement.
7. At least 5 mm of clear nail on the target toenail between the lunular proximal nail fold and the deepest extend of the onychomycosis.
8. The deepest extend of onychomycosis should not contact the lunula.
9. Besides onychomycosis, patients are in overall good health, or have a condition under stable treatment and are willing to comply with adequate foot care for the duration of the study.
10. Females of childbearing potential must not be pregnant or lactating at baseline (as confirmed by a negative urine pregnancy test with a sensitivity of less than 25 mIU/mL or equivalent units of human chorionic gonadotropin). Women of childbearing potential must agree to the use of a reliable method of contraception (e.g., total abstinence, IUD, a double-barrier method [such as condom plus diaphragm with spermicide], oral, transdermal, injected or implanted non- or hormonal contraceptive), throughout the study. If the female is using a hormonal contraceptive, the same product must be taken for 1 month before baseline and must agree not to replace with some other hormonal contraceptives during the study. A sterile sexual partner is not considered an adequate form of birth control.

All females will be considered to be of childbearing potential unless they:

- Are post-menopausal, defined as women who have been amenorrheic for at least 12 consecutive months, without other known or suspected primary cause.

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- Have been sterilized surgically or who are otherwise proven sterile (i.e., total hysterectomy or bilateral oophorectomy) with surgery at least 4 weeks before baseline. Tubal ligation will not be considered a surgically sterile method.

Female patients of childbearing potential are defined as:

- Women without prior hysterectomy of at least 4 weeks, or who have had any evidence of menses in the past 12 months.
- Females who have been amenorrheic for ≥ 12 months, but the amenorrhea is possibly from other causes, including prior chemotherapy, anti-estrogens or ovarian suppression.

11. Signed informed consent form which meets all current ICH/FDA regulations

9.3.2 Exclusion Criteria

1. Patients under 18 years of age.
2. Females who are pregnant, lactating or likely to become pregnant during the study.
3. Patients with proximal onychomycosis, dermatophytomas, fungal spikes, limited lateral onychomycosis, white superficial onychomycosis or significant dystrophy of the target toenail that in the Investigator's opinion would impair the evaluation of onychomycosis.
4. Patient has total dystrophic or proximal subungal onychomycosis of the target toenail.
5. History or current diabetes and/or peripheral vascular disease.
6. Presence of mycotic spikes or patient has exclusively lateral groove involvement of the target toenail.
7. Patients with distal nail plate thickness of the target toenail greater than 3 mm.
8. Patient had no new nail growth requiring nail trimming in the target toenail over the previous 2 months.
9. Previous treatment for onychomycosis of the toenail within the last 12 months that was unresponsive to treatment.
10. Onychomycosis not caused by a dermatophyte (e.g., mold infection, *Candida spp* or bacterial infection).
11. Patients with a history of a trauma involving nail bed of the target toenail before onset of clinical signs of onychomycosis.
12. Patients with any significant active or past medical condition or abnormal laboratory value or who are required to start a medical therapy that in the opinion of the Investigator would make them unsuitable for study participation or compromise patient safety.

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13. Patients who are unable to reach their infected toenails and administer the study product to affected toes.
14. Patients who are likely to apply toenail polish, cosmetic products or undergo professional pedicures during the study.
15. Current or history of psoriasis or Lichen planus within the previous 12 months.
16. Immunocompromised either because of concomitant disease (e.g., HIV), or ongoing treatment (e.g., chemotherapy), including patients with a history of organ transplant and patients on long-term corticosteroid therapy (refer to paragraph 9.3.3 for use of concomitant corticosteroid therapy).
17. Receipt of any drug as part of a research study within 30 days prior to dosing.
18. Use within 4 weeks before baseline of 1) topical antifungal therapies on the feet, 2) immunomodulators or 3) systemic corticosteroids.
19. Use of topical corticosteroids on the feet within 2 weeks before baseline.
20. Use of systemic antifungal agents for the treatment of onychomycosis or any antifungal with known activity against dermatophytes within the previous 24 weeks.
21. Current evidence of drug abuse or history of drug abuse within 1 year before the first dose, including, in the opinion of the Investigator, history of alcohol abuse or active alcoholism.
22. Inability to understand the protocol requirements, instructions, and study-related restrictions, the nature, scope, and possible consequences of the clinical study.
23. Unlikely to comply with the protocol requirements, instructions, and study-related restrictions, such as uncooperative attitude, inability to return for follow-up visits, and improbability of completing the clinical study.
24. Patient is the Investigator or his/her deputies, research assistant, pharmacist, clinical study coordinator, other staff or relative thereof directly involved in the conduct of the clinical study or employed by the clinical site, or a first-degree relative of a site employee.
25. Patients with previous exposure to the study drug, or with known allergy to the drug or any of its components.

9.3.3 Restrictions during the Study

The following concomitant medications will not be allowed during the study and during the specified washout periods before Visit 1:

Restricted medication	Examples (not comprehensive)	Washout
Systemic antifungals	Sporanox [®] ,	24 weeks

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	terbinafine,	
Topical antifungals on feet	Lotrimin [®] , tea tree oil, crystal violet	4 weeks
Systemic corticosteroids	prednisone, prednisolone	4 weeks
Topical corticosteroids		2 weeks
Immunomodulators	chemotherapy, rheumatoid arthritis drugs	4 weeks

Note: Treatment for tinea pedis or tinea cruris will be allowed during the study, and a topical antifungal medication will be provided to patients as deemed necessary by Investigator.

Occasional short term use of systemic and topical corticosteroids other than the feet is allowed to the extent that, in the opinion of the investigator, does not compromise the study results.

The use of topical corticosteroids on the feet is restricted for the entire study.

The use of intranasal, inhaled or ophthalmic corticosteroids is allowed up to 1 mg/day.

9.3.4 Removal of Patients from the Study

Patients will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the Investigator may withdraw a patient from the study to protect the health of that patient. A patient may also be withdrawn for not complying with study procedures. The clinical report will include all reasons for early withdrawals.

All patients who are randomized will be included in the safety analysis comparing the test and placebo products. If a patient terminates from the study early, all efforts will be made to complete the patient's end of study visit procedures. For early termination the Investigator shall fully document the reason for early termination. Reasons for early termination may include the following:

- Patient withdrew consent
- Significant adverse event that led the Investigator or patient to withdraw for safety reasons
- Non-compliance with protocol requirements/protocol deviation (e.g., use of restricted medication, not following dosing procedures, failure to make scheduled study visits in a timely fashion). A patient may also be withdrawn by the Investigator if:
 - A protocol deviation or intercurrent illness occurs during the conduct of the clinical study, which, in the clinical judgment of the Investigator or after discussion with the Sponsor, may invalidate the clinical study

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- It is discovered that the patient was included in the clinical study in contradiction to the inclusion and exclusion criteria
- Pregnancy
- Significant worsening of onychomycosis such that the Investigator and/or patient believes it is in the best interest of the patient to withdraw from the study and be provided alternative treatment
- Adverse event: if a patient reports symptoms, which are considered unacceptable by the patient or the Investigator, he/she will be withdrawn from the clinical study. The appropriate AE form in the Case Report Form (CRF) will be completed.
- Participant enrolls in another clinical trial, or is found to have previously enrolled in this clinical trial

All reason(s) for premature withdrawal will be recorded. All patients who withdraw or are withdrawn from the clinical study because of an AE, or clinical laboratory abnormality will be followed up at suitable intervals in order to evaluate the course of the AE or laboratory abnormality and to ensure reversibility or stabilization. The subsequent outcomes of these AEs will be recorded in the patient's source file.

Patients who withdraw or are withdrawn after exposure to study product will not be replaced.

9.3.5 Early Terminations and Protocol Deviations

The following rules and conventions will be used for patients who terminate from the study early or are dropped from the study because of protocol deviations.

If a patient terminates from the study early, all efforts will be made to complete Visit 7 study procedures.

Any patient who either requests to be dropped from the study because of lack of therapeutic efficacy or is dropped by the Investigator for lack of therapeutic efficacy will automatically be considered a "clinical failure" irrelevant of their target toenail assessment score at the termination visit.

Any patient who uses any protocol restricted medication specifically for the treatment of their infection will be discontinued from further participation in the study and automatically be considered a "clinical failure" irrelevant of their target toenail assessment score at the last visit.

Any patient who uses any protocol restricted medication NOT specifically for the treatment of their onychomycosis will be discontinued from further participation in the study. The patient will be considered a "clinical cure" or "clinical failure" based on the target toenail assessments at the termination visit.

Any patient who is dropped for any other reason, other than those covered above, had a positive baseline culture and makes at least one post-baseline visit where clinical assessments for target toenail are performed and/or a KOH and/or mycological culture result is obtained, will be

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included in the ITT. Examples would include: failure to use the study products as required by the protocol (see section 9.4.5), patient withdraws consent for continued participation, patient fails to make study visits on a timely basis.

9.3.6 Clinical Study Termination

The clinical study may be terminated if:

- The Sponsor considers the applied dose of the study product to be no longer relevant
- The Sponsor decides to terminate the clinical study, in particular because data not known before become available and raise concern about the safety of the patients so that continuation of the clinical study would pose potential risks to the patients

Termination of the clinical study, for any reason, must be mutually agreed upon by the Principal Investigator and the Sponsor, and must be documented. However, clinical study results will be reported according to the requirements outlined in this protocol as far as applicable.

9.4 Treatments

9.4.1 Treatments Administration

Patients will be provided with verbal and written instructions on how to dose. Patients are to begin dosing on Day 1 in the office with a clinic staff member observing.

The following treatments will be assessed in this study:

- **Treatment Group A:** Test treatment for Days 1 – 56 and Placebo treatment for Days 281 – 336
- **Treatment Group B:** Test treatment for Days 1 – 56 and Days 281 – 336
- **Treatment Group C:** Placebo treatment for Days 1 – 56 and Days 281 – 336

Study treatment is to be administered by the patient once daily, preferably in the morning after cleaning the affected area with non-medicated soap and patting dry with soft towel. The nails should be completely dry before applying product. A single dose is approximately 30 µl of topical solution. The material will be applied to toenails with a brush that will provide a maximum volume of up to 50 µl after a single fill. A volume of 30 µl to 50 µl of the solution will cover a single nail and nearby skin, depending on the size of the nail. Daily applications of a 10% concentration will provide between 3 - 5 mg of Novexatin per nail. The date and time of each dose must be recorded in the dosing section of the patient diary.

Details of dose administration

The study products will be administered at home by the patients according to the procedure below. The first dose will be applied by the patient in the clinic at Visit 2, with a clinic staff member observing.

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- Apply the study product at approximately the same time each day, leaving sufficient time post-application for the solution to dry on the nail (the solution will dry in approximately the same time as required for cosmetic nail polish and will be dry to the touch)
- Using the supplied brush, spread a liberal amount of the study product evenly across all toenails on feet with affected toenails and adjacent skin of the toes, working from the outside of the nail inwards to ensure the nail edges have made contact with the solution

9.4.2 Identity of Investigational Product

The following products will be used in this study:

Test: Novexatin[®] 10% Topical Solution (Taro Pharmaceuticals, USA)

Placebo: Placebo (Vehicle) Topical Solution (Taro Pharmaceuticals, USA)

The active ingredient in Novexatin[®] study products is presented as a 100 mg/ml (10%) solution of net peptide of Cyclo [7xArg] for topical application to the surface of the toenail. All study medication will be supplied in capped high-density glass amber bottles with a nylon brush.

All randomized study product will be blinded and packaged in blinded sealed boxes or bags. Each bottle will be identified only by a label bearing the Sponsor name, protocol number, randomization number, treatment duration and a statement that the study product is for Investigational Use Only. The study staff will dispense the study product bottle only to those patients identified by the Investigator. The study staff will instruct the patients on the use and return of study product.

Individual bottles of study product for Visit 2 (randomization) will be packaged in blocks. One block will consist of three boxes of study product containing 2 bottles (#1 & 2) according to the randomization code. Bottles # 3 & 4 will be provided for all active patients at sites before Visit 5. The study product will be provided in three configurations:

- A. bottles #1 & 2 – Test and bottles #3 & 4 – Placebo
- B. bottles #1 & 2 – Test and bottles #3 & 4 – Test
- C. bottles #1 & 2 – Placebo and bottles #3 & 4 – Placebo

The study product will be shipped to each Investigator's site from a centralized pharmacy for the initial shipments. Site to site study product distribution and shipping is allowable in cases approved by the sponsor. The Principal Investigator at each site is responsible for ensuring that all study products are stored in a locked, secure location, with access limited to the Investigator and his/her designee(s). An accurate inventory of the study product will be maintained in accordance with federal regulations.

Once the site has been notified that they may do so, all unused study product and empty or partially used bottles of study product may be returned to the Sponsor or designee.

Storage Conditions:

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Study product will be stored at controlled room temperature, away from direct sunlight exposure, at 25°C (77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F). The Principal Investigator at each site is responsible for ensuring that all study products are stored in a locked, secure location, with access limited to the Investigator and his/her designee(s).

9.4.3 Method of Assigning Patients to Treatment Groups

9.4.3.1 Enrollment

At Visit 2 eligible patients will be randomized to the study and assigned enrollment randomization number. Randomization numbers will consist of a 2-digit site number and 4-digit randomization number. The 4-digit randomization numbers will be assigned in ascending order beginning with the lowest number at each study site.

9.4.3.2 Randomization

The study product will be packaged and blinded by an independent clinical packaging company. The randomization will be generated in blocks of 3, containing the study products in three configurations:

- A. bottles #1 & 2 – Test and bottles #3 & 4 – Placebo
- B. bottles #1 & 2 – Test and bottles #3 & 4 – Test
- C. bottles #1 & 2 – Placebo and bottles #3 & 4 – Placebo.

Three patients worth of study product bottles 1 & 2 will be packed into a larger box. This larger box will be designated “one block” of study product. The study product bottles 1 & 2 will be blinded, packaged and delivered to the study site in blocks at the beginning of the enrollment. Bottles 3 & 4 will be delivered to the study site before Visit 5 (2nd treatment start).

At each Visit 2 and Visit 5 each patient will receive two 5 ml bottles of study product according to the randomization code. Patients will be randomized to a treatment regimen in a blinded fashion by assigning randomization numbers in ascending sequential order starting with the lowest available randomization number at each site. All patients randomized will be identified by initials, date of birth, and a unique six-digit patient number. The first two-digits will identify the Investigator site where the patient was enrolled and the last four will correspond with the randomization number of study product bottle assigned to the patient. A perforated or two-part label will be attached to each of the small sized boxes of study product supplies. Both pieces of the label will include the following information: Protocol number, randomization number, space for patient’s initials, statement that the study product is for investigational use only, space for dispensing date and the Sponsor’s name. In addition all patients will be provided with written instructions on how to use the study product. One part of the label shall remain attached to the box. The other part will be removed prior to dispensing and attached to the study product log.

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9.4.4 Study Blind

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the patient assignment. The patient will be requested not to discuss the appearance of the study product bottle with the Investigator or study staff.

To ensure that information that could potentially bias handling of data is not disclosed, the clinical packaging company will hold the randomization scheme until database lock.

Each bottle will be labeled with a blackout label in order to blind the bottle. Each bottle will be labeled with a two-part, double blind label and will display the following text: "content statement, protocol number, subject number, instructions for use and storage, Sponsor's name, an investigational use statement and warnings: "For Topical Use Only" and "Keep out of reach of children". Part 2 of the label will contain a sealed copy of the randomization scheme (as a scratch off portion of the product label). This label should be detached from the bottle prior to dispensing to the patient and retained in a secure location at the study site, to be opened in case of medical emergency only.

Where possible, the Sponsor and Novum medical monitor should be contacted before breaking the blind for any patient. In the event the blind is broken for any reason Sponsor and Novum should be notified as soon as possible in writing of the details of the occurrence.

At the conclusion of the study, after the database has been locked, each site will be sent the full study randomization scheme that should be retained with the study documents in the event of an FDA Inspection.

The bottles used for all three study products are identical in size, shape and color. A standard label overlay will be used and there is no difference in odor of the products. Therefore, all three products are indistinguishable. This will allow the treatment phase of the study to be conducted under double-blind conditions, such that neither the patient nor the Investigator or study staff members will know the identity of each patient's treatment.

9.4.5 Compliance

Patients will be provided with a diary to record the time and date of dosing, as well as any adverse events or concomitant medications.

Patients are required to administer 75%-125% scheduled doses of study product for each of the two 56-day treatment periods as outlined in table below. If patients missed 4 or more consecutive doses, they will be considered non-compliant. A single dose is equivalent to single application of study product to each toenail (affected and non-affected).

Duration	Scheduled doses	Compliance Criteria	
		not more than 125% (doses)	not less than 75% (doses)
56 days	56	70	42

All used and unused study product bottles will be returned by the patient at each study visit and assessed for drug accountability and treatment compliance. In addition, patient compliance with dosing will be calculated by analyzing the doses recorded in the Patient Diary. If the subject does not return the Patient Diary, patient-reported dosing compliance will be recorded in the source notes and will be used to derive compliance.

9.5 Study Conduct

9.5.1 Visit 1: Day -35 to -1 (Screening)

1. **Informed Consent:** Patients who are willing to comply with study procedures will read and sign the informed consent form.
2. **Inclusion/Exclusion Criteria:** Patients will be screened for eligibility based on inclusion/exclusion criteria. Those who fulfill all criteria will proceed to the steps below.
3. **Demographics and Medical History:** Review patient's demographic and medical history. Review patient's use of medications within the last 6 months.
4. **Physical Examination:** A general physical examination will be conducted to assess a good, general health status of the patient; examination of the lower extremities must be included.
5. **Vital Signs:** Blood pressure (BP), heart rate (HR), respiratory rate (RR) and body temperature will be recorded.
6. **Clinical Laboratory Tests:** Blood and urine sample for safety lab tests will be taken. The tests are outlined in Appendix D.
7. **Urine Pregnancy Test:** For women of childbearing potential, a urine pregnancy test will be performed to evaluate pregnancy. Any patient with a positive pregnancy test will not be allowed participation in the study.
8. **KOH Test:** Microscopic examination of specimens of affected toenails will be conducted to visualize the presence of pathogenic fungi. Collected nail specimens will be processed on site for KOH slide preparation as outlined in Appendix B.
9. **Fungal Culture Collection:** If the onsite KOH prep test is positive, then the same site on the nail will be processed for fungal culture. All culture plates will be sent to central laboratory for testing. If the culture result is negative, the patient can be rescreened.
10. **Investigator Clinical Assessment:** Perform an examination of the infected feet/toenail(s). The number of toenails infected should be counted. Nail appearance will be recorded.

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11. **Visual Assessment:** The toenail that the investigator considers meeting Inclusion/Exclusion criteria will be identified and the investigator will assess the nail involvement. If the subject has a bilateral infection of both big toenails, both toenails can be used to assess nail involvement.

12. Schedule Visit 2.

9.5.2 Visit 2: Day 1 (Baseline and Randomization / 1st Treatment start)

1. **Inclusion/Exclusion Criteria:** Patients will be questioned to ensure they continue to meet all inclusion/exclusion criteria for the study. Patients with a negative result for the fungal culture test on Visit 1 will receive appointment cancellations for Visit 2, and will not participate in the study.
2. **Concomitant Medications:** Review and record since Visit 1.
3. **Urine Pregnancy Test:** For women of childbearing potential, a urine pregnancy test will be performed to evaluate pregnancy. Any patient with a positive pregnancy test will not be allowed to participate in the study.
4. Trimming target nail, if needed.
5. **Investigator Clinical Assessment:** Perform a foot/toenail exam. Infected toenail count will be recorded. Nail appearance will be recorded.
6. **Evaluation of Toenail Appearance and Condition:** The investigator and patients will perform a visual assessment and rate target toenail appearance and condition per Appendix A.
7. **Visual Assessment:** The target toenail involvement will be recorded. The toenail (one of the two great toenails) that meets inclusion/exclusion criteria will be identified and designated as the target toenail and used for all further evaluations.
8. **Planimetry Assessment:** Appropriate photographic documentation will be obtained in accordance with Canfield Scientific Inc. guidelines for the planimetry assessment.
9. **Dispense Randomized Study Product and Administration Instructions:** Patients will be randomly assigned to one of the three **treatment groups** of the study, and will receive a randomization number. Qualified patients will be provided with two bottles of randomized study product. A set of instructions to apply the study product at home will be provided, along with supplies including standardized non-medicated bar of soap and towel.
10. **Dispense Patient Diary:** A diary along with instructions to record dose frequency and timing, adverse events and concomitant medications will be provided.
11. **Administer First Dose:** Clinic staff member will observe the first application of study product by the patient in the clinic.

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12. **Adverse Events:** Any adverse events following first dose will be recorded by patient in diary.

13. Schedule Visit 3.

9.5.3 Visit 3: Day 57 ± 4 (1st Treatment completion; the last dose will be on Day 56)

1. **Urine Pregnancy Test:** For women of childbearing potential, a urine pregnancy test will be performed to evaluate pregnancy. Any patient with a positive pregnancy test will not be allowed participation in the study.

2. **Clinical Laboratory Tests:** Blood and urine sample for safety lab tests will be taken. The tests are outlined in Appendix D.

3. **Vital Signs:** BP, HR, RR and body temperature will be recorded.

4. **Collect Study Product Bottles:** Bottles will be inspected for intentional tampering.

5. **Collect/Review Patient Diary:** Collect patient diary and review for concomitant medications, adverse events and compliance with the protocol.

6. Dispense new diary.

7. **Application Site Reactions:** The Investigator will evaluate the patient for local application site reactions and question patient regarding symptoms experienced since the previous visit based on the scale provided in Appendix C.

8. Trimming target nail, if needed.

9. **Investigator Clinical Assessment:** Perform a foot/toenail exam. Record infected toenail count and nail appearance.

10. **Evaluation of Toenail Appearance and Condition:** The investigator and patients will perform a visual assessment and rate target toenail appearance and condition per Appendix A.

11. **Visual Assessment:** The investigator will assess the nail involvement of the “target toenail”.

12. **Planimetry Assessment:** Appropriate photographic documentation will be obtained in accordance with Canfield Scientific Inc. guidelines for the planimetry assessment.

13. Place all records/ documents in patient’s source folder.

14. Schedule Visit 4.

9.5.4 Visit 4: Day 141 ± 7 (Interim)

1. **Urine Pregnancy Test:** For women of childbearing potential, a urine pregnancy test will be performed to evaluate pregnancy. Any patient with a positive pregnancy test will not be allowed participation in the study.

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2. **Collect/Review Patient Diary:** Collect patient diary and review for concomitant medications, adverse events and compliance with the protocol.
3. Dispense new diary.
4. **Application Site Reactions:** The Investigator will evaluate the patient for local application site reactions and question patient regarding symptoms experienced since the previous visit based on the scale provided in Appendix C.
5. Trimming target nail, if needed.
6. **Investigator Clinical Assessment:** Perform a foot/toenail exam. Record infected toenail count, target toenail involvement and nail appearance.
7. **Evaluation of Toenail Appearance and Condition:** The investigator and patients will perform a visual assessment and rate target toenail appearance and condition per Appendix A.
8. **Visual Assessment:** The investigator will assess the nail involvement of the “target toenail”.
9. **Planimetry Assessment:** Appropriate photographic documentation will be obtained in accordance with Canfield Scientific Inc. guidelines for the planimetry assessment.
10. **KOH Test:** Microscopic examination of specimens of affected toe nails will be conducted to visualize the presence of pathogenic fungi. Collected nail specimens will be processed on-site for KOH slide preparation as outlined in Appendix B.
11. **Fungal Culture Collection:** A sample for mycological testing should be obtained irrelevant of the results of the KOH stain. All culture plates will be sent to central laboratory for testing.
12. Place all records/ documents in patient’s source folder.
13. Schedule Visit 5.

9.5.5 Visit 5: Day 281 ± 14 (2nd Treatment start)

1. **Urine Pregnancy Test:** For women of childbearing potential, a urine pregnancy test will be performed to evaluate pregnancy. Any patient with a positive pregnancy test will not be allowed participation in the study.
2. **Collect/Review Patient Diary:** Collect patient diary and review for concomitant medications, adverse events and compliance with the protocol.
3. Dispense new diary.
4. **Vital Signs:** BP, HR, RR and body temperature will be recorded.
5. Trimming target nail, if needed.

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6. **Investigator Clinical Assessment:** Perform a foot/toenail exam. Record infected toenail count, target toenail involvement and nail appearance.
7. **Evaluation of Toenail Appearance and Condition:** The investigator and patients will perform a visual assessment and rate target toenail appearance and condition per Appendix A.
8. **Visual Assessment:** The investigator will assess the nail involvement of the “target toenail”.
9. **Planimetry Assessment:** Appropriate photographic documentation will be obtained in accordance with Canfield Scientific Inc. guidelines for the planimetry assessment.
10. **Application Site Reactions:** The Investigator will evaluate the patient for local application site reactions and question patient regarding symptoms experienced since the previous visit based on the scale provided in Appendix C.
11. **Dispense Randomized Study Product and Administration Instructions:** Qualified patients will be provided with two bottles of randomized study product. A set of instructions to apply the study product at home will be provided, along with supplies including standardized non-medicated bar of soap and towel.
12. Place all records/ documents in patient’s source folder.
13. Schedule Visit 6.

9.5.6 Visit 6: Day 337 ± 14 (2nd Treatment completion; the last dose should be applied the day before Visit 6)

1. **Urine Pregnancy Test:** For women of childbearing potential, a urine pregnancy test will be performed to evaluate pregnancy. Any patient with a positive pregnancy test will not be allowed participation in the study.
 2. **Collect/Review Patient Diary:** Collect patient diary and review for concomitant medications, adverse events and compliance with the protocol.
 3. Dispense new diary.
 4. **Vital Signs:** BP, HR, RR and body temperature will be recorded.
 5. **Collect Study Product bottles:** Bottles will be inspected for intentional tampering or un-blinding.
 6. Trimming target nail, if needed.
 7. **Investigator Clinical Assessment:** Perform a foot/toenail exam. Record infected toenail count, target toenail involvement and nail appearance.
 8. **Evaluation of Toenail Appearance and Condition:** The investigator and patients will perform a visual assessment and rate target toenail appearance and condition per Appendix A.
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9. **Visual Assessment:** The investigator will assess the nail involvement of the “target toenail”.
10. **Planimetry Assessment:** Appropriate photographic documentation will be obtained in accordance with Canfield Scientific Inc. guidelines for the planimetry assessment.
11. **Application Site Reactions:** The Investigator will evaluate the patient for local application site reactions and question patient regarding symptoms experienced since the previous visit based on the scale provided in Appendix C.
12. Place all records/ documents in patient’s source folder.
13. Schedule Visit 7.

9.5.7 Visit 7: Day 365 ± 14 (4 weeks post-treatment or Early Termination)

1. **Urine Pregnancy Test:** For women of childbearing potential, a urine pregnancy test will be performed to evaluate pregnancy. Any patient with a positive pregnancy test will not be allowed participation in the study.
2. **Clinical Laboratory Tests:** Blood and urine sample for safety lab tests will be taken. The tests are outlined in Appendix D.
3. **Collect/Review Patient Diary:** Collect patient diary and review for concomitant medications, adverse events and compliance with the protocol.
4. **Physical Exam:** The Investigator will perform a general physical exam for each patient and any significant findings will be noted. The physical exam, at a minimum, must include an examination of the lower extremities.
5. **Vital Signs:** BP, HR, RR and body temperature will be recorded.
6. Trimming target nail, if needed.
7. **Investigator Clinical Assessment:** Perform a foot/toenail exam. Record infected toenail count, target toenail involvement and nail appearance.
8. **Evaluation of Toenail Appearance and Condition:** The investigator and patients will perform a visual assessment and rate target toenail appearance and condition per Appendix A.
9. **Visual Assessment:** The investigator will assess the nail involvement of the “target toenail”. If the nail involvement does not reach zero at the final visit, the investigator will visually assess the nail involvement based on the following range:
 - 0%
 - > 0-5%
 - 6-9%
 - 10-35%
 - > 35%

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10. **Planimetry Assessment:** Appropriate photographic documentation will be obtained in accordance with Canfield Scientific Inc. guidelines for the planimetry assessment.
11. **Application Site Reactions:** The Investigator will evaluate the patient for local application site reactions and question patient regarding symptoms experienced since the previous visit based on the scale provided in Appendix C.
12. **KOH Test:** Microscopic examination of specimens of affected toe nails will be conducted to visualize the presence of pathogenic fungi. Collected nail specimens will be processed on-site for KOH slide preparation as outlined in Appendix B.
13. **Fungal Culture Collection:** A sample for mycological testing should be obtained irrelevant of the results of the KOH stain. All culture samples will be sent to central laboratory for testing.
14. Place all records/ documents in patient's source folder.

9.6 Study Procedures

9.6.1 Informed Consent

No patient will be entered into the study without reading, understanding, and signing an informed consent. For illiterate patients, verbal consent should be obtained in the presence of and be countersigned by a literate witness. If any other language is required, translation will be performed by a certified translator.

9.6.2 Demographics

At Visit 1, each patient shall be required to provide basic demographic information: date of birth, gender, ethnicity and race.

9.6.3 Medical History

At Visit 1, patients will be questioned about medical history, including acute and chronic medical history and medical history relevant to their onychomycosis, as well as all concomitant medication use within the previous 6 months.

9.6.4 Vital Signs

The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate) at specified visits.

9.6.5 Physical Exam

At each specified visit, the Investigator will perform a general physical exam for each qualified patient and any significant findings will be noted. The general physical exam is intended to assess a good, general health status of the patient and must include an examination of the lower extremities.

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9.6.6 Concomitant Medication Use

At Visit 1, patients will be questioned about current and concomitant medication use over the previous 6 months. At all other clinic visits, patients will be questioned about ongoing or new concomitant medication use.

9.6.7 Pregnancy Test

Urine pregnancy tests on women of childbearing potential will be performed at each clinic visit during the treatment period. The test must be negative for the patient to be eligible for inclusion in the study. If the patient is of non-childbearing potential, the source document must list the reason why she is of non-childbearing potential.

Patients with a positive pregnancy test during screening will not be enrolled in the study. Patients who report they have become pregnant or who have a positive pregnancy test at the end of study visit will be followed to completion of the pregnancy. The pregnancy will be reported as an AE.

9.6.8 Dispensing Study Product

At Visit 2 (Randomization) after the Investigator has determined that the study patient meets the inclusion/exclusion criteria for the study a clinic staff member will dispense two bottles (1 & 2) of the study product to the patient using the lowest patient randomization number available at that investigative site. Study product should not be dispensed at Visit 2 until it is confirmed that the patient meets all the inclusion/ exclusion criteria including positive results from the mycological culture. The patient will be dispensed bottles 3 & 4 of the study product at Visit 5.

9.6.9 Collecting Study Product

At Visits 3 and 6 the study product bottles will be collected and inspected for evidence of tampering.

9.6.10 Dosing Instructions and Diary

Patients will be given a diary with instructions at each clinic visit from Visit 2 to Visit 6. Patients will be asked to record the time and date of each dose, AEs, and concomitant medications throughout the study. The diary will be reviewed at Visits 3-7 by the study staff.

9.6.11 Dosing Compliance

Patient diaries will be collected at Visits 3-7 so that the study staff may check compliance. Patients are required to administer 75%-125% scheduled doses of study product for each of the two 56-day treatment periods as outlined in table below. If patients missed 4 or more consecutive doses, they will be considered non-compliant. A single dose is equivalent to single application of study product to each toenail (affected and non-affected). At the end of the study they will be retained in the patient's file as source documentation.

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9.6.12 Target Nail Trimming

Patients will be expected to keep toenails trimmed as part of their standard foot care. The target nail will be trimmed prior to visual assessments if, in the opinion of the Investigator, the length of the nail could impact the assessment of onychomycosis.

9.6.13 Visual Assessment and Planimetry

At screening, both big toenails can be evaluated for nail involvement if the subject has a bilateral infection of the big toenails. At Visit 2, the target toenail will be identified and nail involvement of the target toenail over time will be monitored visually by an investigator at every visit. If the nail involvement does not reach zero at the final visit, the investigator will visually assess the nail involvement based on the following range:

- 0%
- > 0-5%
- 6-9%
- 10-35%
- > 35%

At Visit 2 and all subsequent visits, the target toenail will also be monitored by planimetry. Appropriate photographic documentation of the target toenail will be obtained for the planimetry assessment at Visit 2 and submitted to Canfield Scientific, Inc. to determine the nail involvement. At all subsequent visits, appropriate photographic documentation of the same target toenail will be obtained and submitted to Canfield Scientific, Inc. to determine the nail involvement. Photographs of the target toenail will be collected using the procedures provided by Canfield Scientific, Inc. The photographs from each visit will be processed and reviewed by an independent panel. An image analysis will be conducted and numerical values for the % affected (in terms of surface affected for both the healthy and pathologic area of the target nail) will be reported. The % affected will be used to judge Satisfactory Clinical Cure.

9.6.14 Investigator Clinical Assessment:

An investigator will perform an exam of foot/toenail at each visit. Infected toenails will be counted and recorded. Nail appearance will be recorded.

9.6.15 Evaluation of Toenail Condition/Appearance:

The toenail, one of the two great toenails, that the investigator considers to be the most appropriate as the target toenail will be identified and designated as the "target toenail" at Visit 2 and used for evaluations.

The overall appearance of the target toenail over time will be monitored during the study:

1. Self-assessed by patients. The results of the self-assessment will be recorded by the patient before beginning therapy at Visit 2 and at all subsequent visits. Patients will use a 5-point scale (see Appendix A) for target toenail appearance.

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2. Assessed by Investigator: Investigators will rate the status of the target toenail before beginning therapy at Visit 2 and at all subsequent visits. Nail condition/appearance by investigator will be evaluated after nail trimming to the distal groove and before further trimming, if required, for the mycological evaluation. Investigators will use a 5-point scale (see Appendix A) target toenail appearance.

9.6.16 KOH Stain

At screening, a sample from both big toenails can be collected for subjects with a bilateral infection of the big toenails. At subsequent applicable visits, a sample from the target toenail will be collected and a KOH stain performed using standardized methodologies that will be provided to the Investigators.

If at Visit 1 the result of the KOH stain is negative then no further assessments need be conducted on this patient as they will not be eligible for inclusion. If at Visit 1 the KOH stain test is positive then a sample for mycological culture must be obtained (see Section 9.6.14) to confirm the result.

At Visits 4 and 7, a sample for KOH and mycological culture should be obtained so that subsequent analysis of the correlation between KOH stain and mycological culture results can be performed.

9.6.17 Sample for Mycological Culture

If at Visit 1 the result of the KOH stain is negative then no sample for mycological testing should be taken from this patient as they will not be eligible for inclusion. If at Visit 1 the KOH stain test is positive then a sample for mycological culture should be obtained to confirm the result.

At subsequent visits when a sample is collected for KOH stain a sample for mycological culture must also be obtained irrelevant of the results of the KOH stain.

At screening, samples for the mycological culture will be collected from the big toenail that resulted in a positive KOH stain. At subsequent visits, samples for mycological culture will be collected from the target toenail using the procedures provided by the central laboratory. The sample will be processed and sent to a central microbiological testing laboratory. It is anticipated that it will take 14 to 30 days for the microbiological laboratory to provide the investigator with the results of the culture. Refer to Appendix B.

9.6.18 Application Site Reactions:

At each visit following randomization the Investigator will evaluate the patient for local application site reactions and question patient regarding symptoms experienced since the previous visit based on the scale provided in Appendix C. Application Site reactions (see Appendix C) will be documented in the Source and CRF.

Application site reactions will not be separately recorded as AEs since they are being captured at each visit for erythema, burning/stinging, erosion, edema, pain, itching or dryness unless the Investigator feels it is appropriate to do so.

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9.6.19 Health Status/Adverse Events

At each visit, starting at Day 1, patients will be questioned regarding any changes in their medical status since their previous visit. New medical conditions or the worsening in severity of any concurrent medical conditions reported at baseline, or since the previous visit will be reported as new adverse events.

9.7 Adverse Events

The patients will be monitored throughout the study for any Adverse Events. At each visit following screening, patients will be questioned regarding any changes in their medical status since their previous visit. Observed changes during the clinical assessments at each visit, should be reported as adverse events. Each patient will be observed for signs and symptoms of local irritation and documented appropriately.

AEs will be collected through both solicited and unsolicited means and subsequently coded in tabular form using the MedDRA (Version 19 or higher) Adverse Event Dictionary. The patients will be encouraged to report signs, symptoms, and any changes in health to the clinic staff. Severity of each AE will be determined by the staff based on observation and questioning of the patients. The Investigator will judge the relationship of the event to the study treatments.

9.7.1 Definitions

Adverse Event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease, temporally associated with the use of a medicinal (investigational) product, whether or not related to this product. This includes events not seen at baseline, or worsened even if present at baseline.

Unexpected Adverse Event: An adverse event where the nature or severity of is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Adverse Drug Reaction: All noxious and unintended responses to a medical product related to any dose should be considered adverse drug reactions. The response to a 'medical product' means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Pregnancy: Female patients of childbearing potential must have been using and must agree to continue to use accepted methods of birth control, throughout the study. All female patients are considered to be of childbearing potential unless they are premenarchal, have been surgically sterilized or have been postmenopausal for at least 12 months. Abstinence is an accepted method of birth control. Alternatively, any of the following methods of birth control are acceptable: oral contraceptives, contraceptive patches/implants (e.g., Norplant[®]), Depo-Provera[®], double barrier methods (e.g., condom plus diaphragm with spermicide) or IUD. Prior to study enrollment

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women of childbearing potential must be advised of the importance of avoiding pregnancy during study participation.

A negative result of a urine pregnancy test having a minimum sensitivity of at least 50 mIU/ml for hCG should be obtained, prior to study participation, at Visit 1. Pregnancy testing will also be performed at every study visit and the results of all pregnancy tests (positive or negative) will be documented.

If following initiation of study treatment, it is subsequently discovered that a study patient is pregnant or may have been pregnant at the time of Investigational Product exposure, the Investigational Product will be permanently discontinued. The Principal Investigator must immediately notify the Medical Monitor of this event.

Protocol-required procedures for study discontinuation and follow-up must be performed on the patient. Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the Principal Investigator must report to the sponsor follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of eight weeks after birth.

9.7.2 Severity of Adverse Event

The severity of the adverse event will be graded by the Investigator using the following criteria as guidelines:

- MILD: Awareness of symptom but does not interfere with routine activities
- MODERATE: Discomfort sufficient to interfere with routine activities
- SEVERE: Impossible to perform routine activities

9.7.3 Relationship of Adverse Event

- NOT RELATED: Any AE that is clearly not related to use of the study product.
- POSSIBLE: The association of the AE with the study product is unknown; however, a relationship between the drug and event cannot be ruled out.
- PROBABLE: There is reasonable temporal relationship between the use of the study product and the AE. Based upon the Investigator's clinical experience, the association of the event with the study product seems likely.
- DEFINITE: The AE occurs following the application of the study product and it cannot be reasonably explained by any other known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of treatment administered to the patient. It disappears or decreases upon discontinuation of the study product and reappears on a re-challenge of the study product.

9.8 Serious Adverse Events

9.8.1 Definition

Serious Adverse Event: an Adverse Event or suspected adverse reaction is considered "Serious" if, in the view of either the Investigator or Sponsor, it results in the following outcomes:

1. Results in death: includes all deaths, even those that appear to be completely unrelated to study treatment (e.g., car accident where patient is a passenger).
2. Is life-threatening: in the view of the Investigator, the patient is at immediate risk of death at the time of the event.
3. Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life).
4. Requires inpatient hospitalization or prolongation of existing hospitalization.
5. Causes congenital anomaly or birth defect.
6. Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the serious outcomes listed above (e.g., intensive treatment in an emergency room, convulsions that do not result in hospitalizations). Emergency Room visits that require medical or surgical intervention to prevent one of the other serious outcomes listed above are considered a Serious Adverse Event.

9.8.2 Reporting

Adverse events which are evaluated by the Investigator as "Serious" will be reported to the Sponsor within 24 hours, and the IRB as soon as is practically possible, preferably within 24 hours, whether or not they are considered expected or drug-related. All Serious Adverse Events will be reported as required. All Serious Adverse Events encountered during the study will be reported on the appropriate form and summarized in the final report.

Any serious or unexpected adverse events should be reported to Novum within 24 hours. Following is the contact information:

Gail Gongas
Vice President, Clinical Trials
Cell Phone 412-606-1603
Phone 412-363-3300 x 522
Fax 412-291-3171

Or

Paolo Maria Fanzio, MD
Medical Monitor

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Phone 412-363-3300 x 597

Fax 412-924-0522

Novum will report any Serious Adverse Event to Taro Pharmaceuticals U.S.A., Inc.

Documentation of serious or unexpected adverse events and follow up information should be sent to Taro's SAE Coordinator and Taro's Drug Safety Manager within 24 hours from reporting the event by the Investigator. Following is the contact information:

Taro SAE Coordinator:

Danielle Simpson
Coordinator, Clinical Operation
Taro Pharmaceuticals USA Inc.
Tel: 914-345-9001 ext.6234
Email:
danielle.simpson@taro.com

Taro Drug Safety Manager:

Margo Wyatt, RN, BSN,
Associate Director, Drug Safety Taro
Pharmaceuticals U.S.A., Inc.
Tel: 914-345-9001 Ext. 6758
Email: margo.wyatt@taro.com and
taropvus@taro.com

Under 21 CFR 320.31(d) (3), the Sponsor or CRO must inform other investigators involved in the study of the occurrence of the Serious AEs. The Sponsor must inform appropriate agencies as required once becoming aware of the occurrence of the Serious AEs.

10.0 STATISTICAL METHODS

10.1 Statistical Plan

A statistical analysis plan, detailing the intended statistical analysis of the study data, will be prepared as a separate document and finalized before database lock. Any deviation from the original statistical plan will be described and justified in the final report, as appropriate. The procedure for accounting for missing, unused and spurious data will be included in the Statistical Analysis Plan (SAP). All statistical analysis will be conducted using SAS[®], Version 9.4 or higher.

10.2 Determination of Sample Size

The primary statistical analysis of interest is a comparison of the rates of therapeutic cure (as defined by "clinical cure" AND "mycological cure") of Novexatin[®] 10% topical solution to the rate of therapeutic cure of placebo in the Intent-to-Treat Population (ITT). The rate of therapeutic cure for the Novexatin[®] 10% topical solution 8-week regimens is expected to be approximately 49%. The rate of therapeutic cure for placebo is expected to be approximately 21%. Approximately 46 patients in each treatment group in the ITT population will provide over 80% power to show a difference at $p < 0.05$ (two-sided Z test and a pooled response rate for the standard error of the difference in proportions) between each of the active treatment groups and the placebo group. To allow for a 23% drop-out rate, a total of 180 patients will be enrolled in the study, with up to 60 patients in each of the treatment groups.

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10.3 Study Populations

10.3.1 Intent-to-Treat Population (ITT)

- All randomized patients who applied at least one dose of assigned study product
- Had a positive mycological culture screening (Visit 1)

The primary analyses will be conducted on the ITT population.

Patients who return randomized product bottles with evidence of intentional tampering or unblinding will be excluded from the ITT population and included in the Safety population.

10.3.2 Safety Population

All patients who were randomized and received study product will be included in the Safety population.

10.4 Baseline Comparability

Baseline comparability of all treatment groups will be evaluated separately in the ITT and Safety populations. The following baseline demographics (determined from their initial study visit) will be evaluated:

- Age (years)
- Gender (male/female)
- Ethnicity (Hispanic/non Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native, Other)

Descriptive statistics by treatment group will be presented.

10.5 Efficacy Endpoints

The primary endpoint is the proportion of patients in each treatment group with a complete therapeutic cure of onychomycosis of the target toenail assessed at each of two test-of-cure visits (Day 141 and Day 365).

The secondary endpoint-1 is the proportion of patients in each treatment group with a complete or almost complete therapeutic cure of onychomycosis of the target toenail assessed at each of the two test-of-cure visits (Day 141 and Day 365).

The secondary endpoint-2 is the proportion of patients in each treatment group with a mycologic cure of the target toenail assessed at each of the two test-of-cure visits (Day 141 and Day 365).

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The secondary endpoint-3 is the proportion of patients in each treatment group with a complete clinical cure of the target toenail assessed at each of three test-of-cure visits (Day 141, Day 281 and Day 365).

The secondary endpoint-4 is the proportion of patients in each treatment group with a satisfactory clinical cure of the target toenail assessed at each of three test-of-cure visits (Day 141, Day 281 and Day 365).

Complete therapeutic cure is defined as both complete clinical and mycological cure of the target toenail

Almost complete therapeutic cure is defined as both mycological and satisfactory clinical cure of the target toenail

Mycological cure is defined as a negative KOH test **and** a negative fungal culture.

Complete clinical cure is defined as 0% nail involvement.

Satisfactory clinical cure is defined as $\leq 5\%$ of the target toenail involvement.

10.6 Efficacy Analyses

The ITT population will be used to evaluate the efficacy of Novexatin[®] 10% topical solution for the 8-week treatment regimens in Groups A, B and C.

Descriptive statistics will be summarized for the primary and secondary endpoints (including planimetry data) by study group. As this is a multi-centered study, results may also be presented by study site.

In order to preserve an overall type-I error (alpha) of 5% for evaluation of complete and almost complete therapeutic cure, complete and satisfactory clinical cure and mycologic cure, a hierarchical evaluation scheme will be employed for the primary and secondary endpoints. The four comparisons of interest for the primary endpoint and the secondary endpoints -1 and -2 are:

1. Group B versus Group C – at the test-of-cure visit at Day 365
2. Group A versus Group C – at the test-of-cure visit at Day 365
3. Group B versus Group A – at the test-of-cure visit at Day 365
4. (Group A + Group B) versus Group C – at the test-of-cure visit at day 141

The five comparisons of interest for the secondary endpoints -3 and -4 are:

1. Group B versus Group C – at the test-of-cure visit at Day 365
2. Group A versus Group C – at the test-of-cure visit at Day 365
3. Group B versus Group A – at the test-of-cure visit at Day 365
4. (Group A + Group B) versus Group C – at the test-of-cure visit at Day 281
5. (Group A + Group B) versus Group C – at the test-of-cure visit at Day 141

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Statistical testing will begin with comparison 1. If statistical significance is attained with comparison 1 ($p < 0.05$), then a claim of superiority for comparison 1 can be made and the next comparison in the hierarchical evaluation scheme can be tested for statistical significance. If statistical significance is not attained for comparison 1 ($p \geq 0.05$), then testing of all subsequent comparisons is stopped. The hierarchical, conditional-stepwise evaluation scheme allows for each comparison to be evaluated at the 5% level, while preserving an overall type I error rate of no more than 5%. For the proportion of patients in each treatment group with a complete and almost complete therapeutic cure, complete and satisfactory clinical cure and mycological cure of onychomycosis of the target toenail, the statistical analysis for superiority will be conducted using two-sided Z-Tests and a pooled response rate for the standard error of the difference in proportions for each comparison of interest. The primary and secondary analyses will be performed using an observed case (OC) analysis in the ITT population. Patients discontinued because of lack of treatment effect will be included in the primary analysis as treatment failures.

The following two sensitivity analyses will also be performed on the primary efficacy endpoint in the hierarchical, conditional-stepwise evaluation scheme:

1. Analysis will be performed also including patients without an assessment at Day 365 \pm 14. Patients with missing data at Day 365 \pm 14 will be considered therapeutic failures.
2. Analysis will be performed also including patients without an assessment at Day 365 \pm 14. Patients in Group C with missing data at Day 365 \pm 14 will be treated as therapeutic successes and patients from the Groups A and B with missing data at Day 365 \pm 14 will be treated as therapeutic failures.

Similar sensitivity analyses will be conducted including patients without an assessment at Day 141 \pm 7 for the 4th comparison in the hierarchical, conditional-stepwise evaluation scheme.

Efficacy results will be used to calculate the sample size for the Phase 3 studies.

10.6 Safety Analysis

All study patients who are randomized to the active treatment period of the study, and received study product will be included in the comparative safety analysis. The safety profile of each treatment group will be evaluated by comparing adverse events, application site reactions, vital signs and changes in clinical laboratory results obtained throughout the study. Data will also be collected during the study to compare the results of the KOH stains to the mycological culture results observed during the study.

Adverse events will be classified using standard MedDRA terminology Version 19.0 or higher and summarized by treatment group. Adverse events reported during the study will be tabulated in a summary table listing the type, date of onset, date of resolution, incidence, severity, outcome, action taken, and Investigator's opinion of relationship to the study product. Signs and symptoms of onychomycosis will not be considered adverse

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events, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers that it is in the patient's best interest to be dropped from continued participation in the study and given alternative therapy for their condition.

Should sufficient data exist, adverse event frequencies will be compared between treatments using Fisher's exact test or a similar test.

Concomitant medication use during the randomized treatment period will be tabulated by patient.

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11.0 REGULATORY OBLIGATIONS

11.1 Institutional Review Board

The study protocol, informed consent form, Investigator's Brochure, or package insert (as applicable), and any specific advertising will be submitted to, and approved by, an Institutional Review Board (IRB) before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification of the board's approval along with a description by profession and gender of the board's composition will be provided to the Sponsor.

11.2 Study Documentation

This study will be conducted in compliance with the protocol, Good Clinical Practices (GCPs) and all applicable regulations, including the Federal Food, Drug and Cosmetics Act, US applicable Code of Federal Regulations (title 21), parts 50, 56, 312, 320 and any IRB requirements relative to clinical studies and the Declaration of Helsinki, June 1964, as modified by the 59th World Medical Association General Assembly, October 2008.

The Investigator will permit trial-related monitoring, audits, IRB review and regulatory inspections providing direct access to source data/documents.

11.2.1 Protocol

The Investigator indicated on FDA Form 1572 will act as the Principal Investigator at each study site. Protocols will be noted as approved by placement of the Novum Representative's signature on the cover page. The Sponsor of the study will also approve the protocol by having a study-responsible individual sign the protocol cover page.

11.2.2 Informed Consent

An Informed Consent Form (ICF) that includes all of the relevant elements currently required by FDA and local State regulations will be provided to each prospective study patient before enrollment into the study. The type and method of study, tests to be administered, any potential or possible hazards, and the patient's right to withdraw from the study at any time will be explained to the patients by the Investigator or designee. Once the Investigator or designee is assured that an individual candidate understands the implications of participating in this study, the patient will be asked to give consent by signing and dating in the appropriate areas of the ICF. The Investigator or designee will also sign and date the form, along with a staff member who will sign the ICF as a witness to verify that the patient has indeed received information. For illiterate patients, verbal consent should be obtained in the presence of and be countersigned by a literate witness. If any other language is required, translation will be performed by a certified translator. A copy of the ICF will be provided to the patient.

11.2.3 Protocol and Informed Consent Changes

Revisions to the original protocol will be documented in amendments, incorporated as a preface to the new version and approved by the IRB. Any revision that substantially

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alters the study design or increases potential risk to the patient requires the patient's consent to continue in the study. Revisions to the original ICF will also be approved by the IRB. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and ICF amendments/revisions, along with letters noting IRB approval, will be submitted to the Sponsor.

11.2.4 Source Documents and Case Report Forms

All patients will be identified by initials, date of birth, and a unique patient number. Source documents will be used to record all study-related data. Source document entries will be used to complete Case Report Forms (CRFs). A set of CRFs will be completed for each patient enrolled in the study. All data and CRFs will be reviewed, evaluated and signed by the Investigator, as required.

The original source documents and a copy of the corresponding CRFs will be retained by the Investigator. Patients who terminate early from the study will have end-of-study visit procedures and source/CRF completed.

11.2.5 Drug Accountability

All study product receipt, inventory, dispensing, dosing and reconciliation records will be maintained in compliance with Federal Regulations. The study product will be dispensed to qualified study patients according to established procedures. At the end of the study all used and unused study product will be returned to Novum.

11.2.6 Drug Storage

All study product will be stored at controlled room temperature, away from direct sunlight exposure at 25°C (77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F) in a secure place with access by authorized individuals only. The Investigator will be responsible for maintaining accurate records of product receipt, dispensing, and return. At the end of the study, all partially used and unused study product will be returned to Novum.

11.2.7 Pregnancies

Patients with a positive pregnancy test during screening will not be enrolled in the study. Patients who report that they have become pregnant during the study or have a positive pregnancy test at clinic visit will be followed to completion of the pregnancy. The pregnancy will be reported as an AE.

11.2.8 Withdrawals due to Adverse Events

All AEs, both serious and non-serious, that result in the patient's early withdrawal from the study (either by the patient request or Investigator decision) must be reported to the Novum Medical Monitor.

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11.2.9 Reporting Safety Information to the IRB

The Investigator must promptly report to the Investigator's IRB all unanticipated problems involving risks to patients. This includes death from any cause and all serious adverse events occurring during the study, regardless of the assessed causality.

11.2.10 Record Retention

All drug accountability records, CRFs, source data and related regulatory documents must be retained for at least ten years following completion of the study or for two years after the test product has been approved for marketing by the Food and Drug Administration.

11.2.11 Study Monitoring and Auditing

Novum will be responsible for monitoring the study according to Good Clinical Practice and applicable regulations. Monitoring visits are for the purpose of confirming adherence to the protocol and to verify complete and accurate data collection. The clinical site will make all records associated with the study available to Novum's representative during such visits and audits

The study may be subject to audit by the Sponsor, Sponsor Representative or by regulatory authorities. If such an audit occurs the Investigator must agree to allow access to required patient records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of study procedures.

11.2.12 End of the Trial

The end of the trial is defined as the time at which the last patient has completed their last visit in the study. Upon completion of the study, the study product will no longer be available to the patient but the Investigator can, at their discretion, discuss alternative treatments with the patient.

11.2.13 Clinical Study Report

At the end of the study a full report, in Taro's eCTD format, will be prepared that will include a narrative of the clinical conduct and results of the study, a statistical report including a description of the analysis performed, and other documentation as may be appropriate.

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13.0 APPENDICES

APPENDIX A

The number of toenails infected should be counted. The toenail, one of the two great toenails, that the investigator considers to be the most appropriate as the target toenail will be identified at Visit 2 and designated as the "target toenail" and used for all further evaluations.

Evaluation of Toenail condition/appearance

The overall appearance of the target toenail over time will be monitored during the study:

Self-assessed by patients. The results of the self-assessment will be recorded by the patient before beginning therapy at Visit 2 and at all subsequent visits.. Patients will use a 5-point scale for target toenail appearance:

1. Very Poor
2. Poor
3. Normal/acceptable
4. Good
5. Very good

Assessed by Investigator. Investigators will rate the status of the target toenail before patient begins therapy at Visit 2 and at all subsequent clinic visits. Nail condition/appearance by investigator will be evaluated after nail trimming to the distal groove and before further trimming, if required, for the mycological evaluation. Investigators will use a 5-point scale target toenail appearance:

1. Very Poor
2. Poor
3. Normal/acceptable
4. Good
5. Very good

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APPENDIX B

At screening, a sample from both big toenails can be collected for subjects with a bilateral infection of the big toenails. At subsequent applicable visits, a sample from the target toenail will be collected and a KOH stain performed using standardized methodologies that will be provided to the Investigators.

If a positive fungal culture was not previously confirmed and is not available at a screening, a fungal culture will be obtained from the toenail(s) with a positive KOH wet mount at the screening visit.

The confirmation of a positive potassium hydroxide (KOH) wet mount preparation from target toenail will be conducted at the investigative site.

At all subsequent visits, a nail fungal culture will be obtained at the Target toenail. All mycological samples will be sent to a centralized microbiology laboratory for analysis. The nail sample will be placed in a transport kit provided by the central laboratory. The kit should be sealed according to the directions on the back of the kit. The sample kit should be sent to the central laboratory as instructed in the laboratory manual provided by ACM:

ACM Medical Lab, Inc.

160 Elmgrove Park

Rochester, NY 14624

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APPENDIX C

Application Site Reactions

Monitoring of local tolerability (inflammation) will be based upon established methods including observation of the area of administration and response scoring by the study personnel. Upon the visits to the clinical study site, each patient will be examined for signs of local inflammation and irritation that may be associated with the study products. If any such signs are identified, the response will be graded as follows:

Signs and Symptoms:

Erythema (redness)

Scaling/Dryness

Stinging/Burning

Erosion

Edema (swelling)

Pain

Itching

Grading Scale:

Absent 0

Mild 1 (slight, barely perceptible)

Moderate 2 (distinct presence)

Severe 3 (marked, intense)

Application site reactions will not be separately recorded as AEs since they are being captured at each visit for erythema, burning/stinging, erosion, edema, pain, itching or dryness unless the Investigator feels it is appropriate to do so.

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APPENDIX D

Safety Laboratory variables

Hematology

Hemoglobin
Hematocrit
Red blood cell count (RBC)
White blood cell count (WBC)
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin concentration (MCHC)
Platelet count
Differential white blood cell count
Mean corpuscular hemoglobin (MCH)

Clinical Chemistry

Sodium
Potassium
Calcium
Creatinine
Blood Urea Nitrogen (BUN)
Fasting Glucose
Albumin
Total Bilirubin
Alkaline phosphatase
Gamma-glutamyltransferase (GGT)
Aspartate aminotransferase (AST, SGOT)
Alanine aminotransferase (ALT, SGPT)
Total protein
Direct Bilirubin

Urinalysis

Bilirubin
Glucose
Ketone
Leukocyte Esterase
Nitrite
Occult Blood
pH
Protein
Specific Gravity
Urobilinogen

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APPENDIX E

Investigator Brochure for Novexatin[®]

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APPENDIX F

AMENDMENTS TO THE PROTOCOL

Revisions to the protocol after initial IRB approval are summarized in the amendment below.

Amendment	Date
1	02/24/2016

The following revisions were made to the protocol dated 1/13/2016.

- Updated study schematic to reflect revised procedures
- Updated the study population information.
- Updated the Inclusion/Exclusion verbiage
- Updated the study conduct to include the Planimetry Assessment
- General administrative, formatting and spelling changes made throughout the protocol.
- Updated the restricted medication information and washout timeframes
- Updated the statistical section to include the planimetry involvement.
- Updated procedures for early termination patients.
- Removed the usage of an “Independent Dispenser” throughout the protocol.
- Updated the Identity of Investigational Product
- Updated the verbiage in Study Blind section.
- Updated the study procedures to include Planimetry and Application Site Reaction.
- Updated the verbiage of dosing compliance
- Updated the nail appearance grading scale
- Updated the KOH visit scheduling requirements.
- Minor updates made to the statistical sections to clarify the use of planimetry.
- Addition of Investigator Clinical Assessment description to study procedures
- Added “Place all records/ documents in patient’s source folder” to visits 5, 6 and 7 to be consistent with previous visits.
- Revised application site reactions scale and revised associated verbiage accordingly.

Amendment	Date
2	06/24/2016

The following revisions were made to the protocol dated 02/24/2016.

- Updated the Efficacy Endpoint verbiage
- Updated the Safety Endpoint verbiage

A Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Multi-Site Phase 2b Clinical Study to Assess the Efficacy, Safety and Tolerability of 8-Week Regimens of Novexatin[®], 10% Topical Solution (Taro Pharmaceuticals, USA, Inc.) in Patients with Mild to Moderate Onychomycosis

- Updated the verbiage for the Sample Size Determination
- Updated the Statistical Analysis verbiage throughout the protocol.
- Updated Study Schematic to reflect revised procedures
- Updated the verbiage throughout the protocol to allow for bilateral toenail infections to be evaluated for all Visit 1 procedures.
- Updated verbiage to determine the target toenail at Visit 2.
- Updated verbiage to the Early Terminations and Protocol Deviations section.
- Updated verbiage to the Identify of the Investigational Product.
- Updated Study Conduct and Study Procedure sections to reflect updated procedures.
- General administrative, formatting and spelling changes made throughout the protocol.
- Updated the Study Procedures verbiage
- Updated verbiage to Appendix B to reflect updated procedures.

A Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Multi-Site Phase 2b Clinical Study to Assess the Efficacy, Safety and Tolerability of 8-Week Regimens of Novexatin[®], 10% Topical Solution (Taro Pharmaceuticals, USA, Inc.) in Patients with Mild to Moderate Onychomycosis

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