1 TITLE

A Single Centre, Double Blind, Placebo Controlled, Randomized, Confirmatory Efficacy Study Of Biovite®'s Calmagen™ Dermaceutical Cream & Lotion For The Topical Treatment Of Tinea.

Name of the Investigational Medicinal Product	Biovite®'s Calmagen™ Dermaceutical Cream & Lotion
Indication Studied	Topical Treatment of Tinea
Sponsor Name	Biovite Australia Pty Ltd. ("Biovite"), Unit1, Enterprise Plaza 45 Township Drive West Burleigh, Queensland 4219 AUSTRALIA
Clinical Study Code	MA-CT-09-012 (BIO-005 Part 2)
Development Phase of Study	Phase II
First Patient Enrolled	27 Mar 2010
Last Patient Completed	29 Jan 2011
Study Report Version & Date	Draft Version 0.4, 02-01-2012

This study was conducted in accordance with the Good Clinical Practice guidelines as issued by the International Conference on Harmonization (ICH/135/95, July 2002), Schedule Y, ICMR guidelines and the Declaration of Helsinki (current amendment).

SIGNATURE PAGE

I have prepared this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Author:

Signature	Date
Dr. Girisha R	
Senior Medical Writer	
Manipal AcuNova Ltd.	

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Biostatistician:

Signature	Date
Manigandan Easwaran	
Lead Biostatistician	
Manipal AcuNova Ltd.	

Sponsor's Representative:

Signature	Date
Mr. Peter Johnston	
Managing Director	
Sponsor's Representative	

2 SYNOPSIS

Name of Sponsor/Company: Biovite Australia Pty Ltd, Australia	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: Biovite Calmagen Dermaceutical cream & Lotion		
Name of Active Ingredient: Amycot		

TITLE OF STUDY:

A single centre, double blind, placebo controlled, randomized, confirmatory efficacy study of Biovite®'s Calmagen Dermaceutical cream & lotion for the topical treatment of Tinea

INVESTIGATORS AND STUDY CENTER:

Ethics committee approval was obtained for a single study site (in India). The center actively recruited patients in the study.

Sl No.	Principal Investigator	Study Center
1	Dr. Manoj Parekh	The Apollo Clinic, No. 65,Madhavaraya Mudliar Road, Frazer Town, Bangalore, Karnataka, INDIA

PUBLICATION (REFERENCE):

Not Applicable

STUDY PERIOD:

Date of first enrolment	Date of last patient completed
27 Mar 2010	29 Jan 2011

PHASE OF DEVELOPMENT:

Phase II study

Name of Sponsor/Company: Biovite Australia Pty Ltd, Australia	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: Biovite Calmagen Dermaceutical cream & Lotion		
Name of Active Ingredient: Amycot		

OBJECTIVES:

Primary Objective:

To establish the fungicide profile and test the efficacy of Biovite®'s Calmagen™ Dermaceutical cream & lotion as topical treatment in patients with severe to very severe presentations of Tinea (dermatophyte infection of the skin and/or hair follicles) and Onychomycosis (dermatophyte infection of the nails)

METHODOLOGY:

This was a randomized, placebo-controlled, double blinded and parallel group single centre study. Patients ≥ 18 years of age, with severe tinea of combined severity (itching, erythema and scaling) score of 8 or more or with severe Onychomycosis were randomized to treatment with either placebo or Biovite's Calmagen® Dermaceutical cream or lotion in a 1:1 ratio. Tinea patients were asked to use the treatment cream twice daily for 4 weeks, applied to the affected area of skin. Visits for Tinea patients were scheduled at Screening and at Weeks 1, 2, 3 and 4. Onychomycosis patients were asked to use the treatment lotion twice daily for 12 weeks/3 months, applied over the face of the nail and under and around the margins and cuticle. Visits for Onychomycosis patients were scheduled at Screening and at Months 1, 2 and 3. An optional telephonic follow-up assessment was undertaken at week 2 for the patients with Onychomycosis. An additional observation phase of 12 weeks/3 months was undertaken for Onychomycosis patients only, during which the treatment lotion was applied only once daily.

Clinical determinations of disease severity were done using Investigator Global Assessment (IGA), Tinea scrapings for KOH preparation, fungal culture and live spore counts .The severity/size of Tinea and severity/extent of Onychomycosis were performed by the investigator at scheduled visits.

Name of Sponsor/Company: Biovite Australia Pty Ltd, Australia	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
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Name of Active Ingredient: Amycot		

NUMBER OF PATIENTS

	No. of Patients
Screened	50
Enrolled	28
Completed end of study visit (V5)	28
Included in MITT population	28
Included in PP population	28
Included in the safety population	28

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

The study population consisted of male or female patients aged ≥ 18 years of age with a clinical diagnosis of severe Tinea of combined severity (itching, erythema and scaling) score of 8 or more. Patients with positive KOH and positive fungal culture test were enrolled for the study. Patients who gave written informed consent and consent for taking photograph of the affected region were included in the study.

TEST AND REFERENCE PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Product	**Test**	**Reference**
Active Ingredient	Amycot	Placebo
Dosing Regimen	Twice daily	Twice daily
Route of Administration	Topical	Topical
Manufacturer	**Biovite Australia Pty Ltd, ("Biovite")** Unit1, Enterprise Plaza 45 Township Drive West Burleigh, Queensland 4219, Australia	**Biovite Australia Pty Ltd, ("Biovite")** Unit1, Enterprise Plaza 45 Township Drive West Burleigh, Queensland 4219, Australia

Name of Sponsor/Company: Biovite Australia Pty Ltd, Australia	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
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Dosage Form	Cream	Lotion	Cream	Lotion
Batch/Lot No.	B9566	B9744	B08529	B08528
Treatment ID	A	C	B	D
Manufacture Date	NA	NA	NA	NA
Expiration Date	09/2011	02/2012	09/2010	11/2011

DURATION OF TREATMENT:

Duration of treatment for the patients diagnosed with Tinea was for a period of 4 weeks (with the cream applied twice daily).
Duration of treatment for the patients diagnosed with Onychomycosis was for a period of 3 months (with the lotion applied twice daily) with an observation period of 3 months (with the lotion applied once daily).

CRITERIA FOR EVALUATION:

Efficacy Evaluation:

The primary efficacy endpoint:

- Percentage of patients who had achieved mycological cure since baseline, at the end of the study.

The secondary efficacy endpoints:

Efficacy end-point:

- Reduction in size and severity score of target lesion (size and severity score of Tinea) since baseline, was assessed at the end of study. Reduction in extent and severity score of Target lesion (extent & severity score of Onychomycosis) since baseline, was assessed at the end of study.
- Clinical cure defined as Investigator global assessment response of 'cleared' or 'excellent'.
- Improvement in lesions was assessed by photographic record at baseline and at end of study.

Safety Evaluation:

Safety evaluation included assessment of the following parameters:

- Adverse events
- Assessment of vital signs

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STATISTICAL METHODS

Summary statistics for the key data collected during this study was presented. For categorical variables, the number and percentage of patients in each category was presented. Continuous variables were summarized by presenting the number of observations, median, mean, standard deviation, minimum and maximum values. All patient data was listed.

For the MITT population the proportion of Reduction in the extent and the severity of lesions scale since baseline and KOH preparation, fungal culture, reduction in live spore counts and response to treatment at the end of study was compared between the two groups (Placebo - test).

SUMMARY – CONCLUSIONS

Both the treatment groups were comparable with respect to the demographic characteristics in the MITT population. Majority of study population consisted of males (71.4%) for Tinea and Onychomycosis with mean age of 41.5 years. All the patients were Asians.

All patients (100%) were positive for KOH smear, fungal culture and showed positivity for live spore counts at the screening visit.

Efficacy Results (MITT):

KOH smear, fungal culture and live spore counts at the end of the study were negative in 13 (92.86%), 14 (100.00%) and 14 (100.00%) in the test group for Tinea and Onychomycosis patients. However in the placebo group KOH smear, fungal culture and live spore counts were positive in 14 (100.00%), 8 (57.14%) and 8 (57.14%) patients.

At the end of the study, the mycological cure was achieved in 13 (92.9%) out of 14 patients assessed by KOH smear and in all 14 (100%) patients assessed by fungal culture and by spore counts in the test group. Mycological cure showed significance when the test group was compared with the placebo group with p-value of <0.001, 0.0019 and 0.0019 with respect to KOH smear, fungal culture and live spore count respectively.

At the end of the study, the mean (SD) size of tinea lesion was 3.1 cms and mean (SD) severity score was 2.4 (0.9) in the test group while in the placebo group size and severity scores were 8.8cms (3.7) and 8.1 (1.8) respectively. The reduction in the mean (SD) size and severity score from the screening visit was about 10.2 (3.7) cms and 6.6 (0.5) in the

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test group and 0.8 (3.2) cms and 0.8 (2.0) in the placebo group respectively. Size and severity score of Tinea lesion showed significance when the test group was compared to placebo group with a p-value of <0.0001.

At the end of the study, the mean (SD) percentage of surface area of Onychomycosis lesion was 18.0% and extent and severity score was 1.00 (0.0) in the test group and the in the placebo group, these were 51.0% (4.2) and 2.8 (0.4) respectively. The reduction in the mean percentage of surface area and severity score from the baseline visit was 45% (5.0) and 2.0 (0.0) in the test group and 15% (7.9) and 0.2 (0.4) in the placebo group respectively. Surface area and severity score of Onychomycosis lesion showed significance when the test group was compared to placebo group with a p-value of <0.0001 and 0.0008 respectively.

IGA score of "cleared" was achieved in 3 (33.33%) patients and the IGA response of "excellent" was achieved in 6 (66.67%) patients compared to none in the placebo group for Tinea patients. In Onychomycosis patients, IGA score of "excellent" was achieved in all the 5 (100%) patients compared to none in the placebo group patients. Photographic record showed improvement of tinea lesions in the test group for 9 (100%) patients while in the placebo group, none showed improvement. 5 (100%) patients of Onychomycosisin test group , showed photographic improvement while in the placebo group, none showed any improvement.

Safety Results:

There were no AEs reported in the test group while in the placebo group, a patient reported pain in both the legs, which was mild & not related to the study medication. There were no adverse events reported which was related to the study drug. There were no serious adverse events reported in the study.

Conclusion:
Biovite®'s Calmagen™ Dermaceutical cream & lotion was found to have superior efficacy profile to that of placebo. And it was also found to be safe and tolerable, with comparable safety profile to that of placebo.

DATE OF REPORT

02 Jan 2012

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3.1 LIST OF IN-TEXT TABLES

3.2 LIST OF IN-TEXT FIGURES

3.3 LIST OF POST-TEXT TABLES

4 LIST OF ABBREVIATIONS

LIST OF ABBREVIATIONS	
Abbreviation	**Description**
%	Percentage
°F	°Fahrenheit
AE(s)	Adverse Event(s)
ANOVA	Analysis of Variance
BP	Blood Pressure
CI	Confidence Interval
CM	Concomitant Medication
cms	Centimeters
CRA	Clinical Research Associate
CRF	Case Record Form
CRO	Contract Research Organization
CV	Curriculum Vitae
e.g.	for example
EC	Ethics Committees
GCP	Good Clinical Practices
HIV	Human Immunodeficiency Virus
i.e.	id est (that is)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization - Good Clinical Practice
ICMR	Indian Council of Medical Research
ID	Identification
IEC	Independent Ethics Committee
IGA	Investigators Global Assessment
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention to Treat

KOH	Potassium Hydroxide
Mg	Milligram
MAL	Manipal AcuNova Ltd.
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intention-to-Treat
mL	Milliliters
Mnth	Month
NA	Not Available
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PIC	Patient Identity Code
PP	Per Protocol
PT	Preferred Term
QA	Quality Assurance
SAE(s)	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
SOP	Standard Operating procedure
V	Visit
WHO – DD	World Health Organization Drug Dictionary
Wks	Weeks
WMA	World Medical Association

5 ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD

The version 1.0 of protocol of study code MA-CT-09-012 dated 4 Dec 2009 and Informed Consent Form (ICF) dated 9 Dec 2009 were reviewed and approved by all the appropriate Ethics Committees (EC) prior to enrollment of the patients into the study. The names and address of the single study center along with EC approval letter and EC member details for each study site are provided Appendix 16.1.3.

5.2 ETHICAL CONDUCT OF THE STUDY

This study was carried out in accordance with the principles of Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, revised by the WMA General Assembly, Tokyo 2004 and Seoul 2008), International Conference on Harmonization (ICH) recommendation on Good Clinical Practice (GCP) (ICH/135/95, July 2002), 'Indian GCP', 'Schedule Y' of Indian Drugs and Cosmetics Rules 1945, and Ethical guidelines for biomedical research on human participants 2006, issued by ICMR.

5.3 PATIENT INFORMATION AND CONSENT

The investigator was responsible for obtaining signed and dated ICFs from the patients before any study specific procedures were performed within 45 days prior to study start. The patients were given adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Patients were given an opportunity to ask any questions and all the queries were clarified by the Principal Investigator / Co-investigator before decision making. The ICF described the study procedures and the possible potential hazards in non technical terms in conformity with regulatory requirements.

The ICFs (adult ICFs and assent forms for minor) were available in English and other required 4 native languages (i.e. Hindi, Marathi, Kannada and Tamil). The ICF and assent form was translated in 4 languages from English and back translated to English by a certified translator. The patients were required to read and sign a consent form summarizing the discussion. The original copies of the signed and dated ICFs were retained in the institution's records, and were available for inspection by representatives of the sponsor, or representatives from competent authorities. Patients were given a copy of their written, signed and dated ICFs.

Copies of the ICF in English and other 4 native languages (i.e. Hindi, Marathi, Kannada and Tamil) with translation and back translation certificates are provided in Appendix 16.1.3.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This clinical study was sponsored by Biovite Australia Pty Ltd, ("Biovite"). At the center, the principal investigator had the overall responsibility for the safety of patients in the study. The list of participating investigators and the study site details are provided in Table 1

Table 1: Investigator and Study Center

Serial No.	Principal investigator	Study Center
1	Dr. Manoj Parekh	The Apollo Clinic No. 65,Madhavaraya Mudliar Road, Frazer Town, Bangalore, Karnataka, INDIA

Other Study Team & Study Facility Details

The Contract Research Organization, Manipal AcuNova Limited (MAL) was responsible for project management, clinical and medical monitoring, clinical data management, statistical analyses and preparation of the clinical study report. The clinical trial supplies along with the investigational products (IP) were provided by Biovite Australia Pty Ltd, ("Biovite") to MAL. MAL distributed the IP to the study site, and the management of IP at study site was performed by the study site unblinded pharmacist. Details of the study team and study facility are provided in **Table 2**.

Table 2: Study Team and Facilities

Sponsor	Biovite Australia Pty Ltd, ("Biovite") Unit1, Enterprise Plaza 45 Township Drive West Burleigh, Queensland 4219 Australia
Sponsor's Authorized Representative	Mr. Peter Johnston Managing Director Biovite Australia Pty Ltd PO Box 364 West Burleigh, Queensland 4219, Australia
Contract Research Organization (CRO)	Manipal AcuNova Ltd. Mobius Towers, SJR - I park, EPIP Zone, Whitefield, Bangalore - 560066 Tel: +91-80-6691 5700; Fax: +91-80-6691 5719 www.ecronacunova.com
Clinical Study Project Manager (CRO)	Mr. Rakesh Naranbhai Dadhania Project Manager Manipal AcuNova Limited Mobius Towers, SJR - I park,

	EPIP Zone, Whitefield, Bangalore - 5600 66 Tel: +91(0)80 6691 5700, Fax: +91(0)80 6691 5719 Mobile: +91 (0) 9945503701
Medical Monitor (CRO)	Dr Girisha R, MBBS, DVL Manipal AcuNova Limited Mobius Towers, SJR - I park, EPIP Zone, Whitefield, Bangalore - 560066 Tel: +91 (0) 80 6691 5776 Fax: +91 (0) 80 6691 5719 Mobile : +91 (0) 9743149942
Protocol Author	Dr Girisha.R, MBBS, DVL Medical Writer Manipal AcuNova Limited Mobius Towers, SJR - I park, EPIP Zone, Whitefield, Bangalore - 560066 Tel: +91 (0) 80 6691 5700 Fax: +91 (0) 80 6691 5719
Biostatistician	Kanimozhi A Lead Biostatistician Manipal AcuNova Ltd Mobius Towers, SJR - I park, EPIP Zone, Whitefield, Bangalore - 5600 66 Tel: +91 (0) 80 6691 5715 Fax: +91 (0) 80 6691 5719 Mobile: +91 (0) 9986917958
Data Management	Nagaraja Hegde Head, Information Technology & Data Management, Manipal AcuNova Ltd., Mobius Towers, SJR - I park, EPIP Zone, Whitefield, Bangalore - 560066 Tel: +91 (0) 80 6691 5700; Fax: +91 (0) 80 6691 5719

The details of the study personnel were documented in the raw data sheets as log of staff at the trial sites. The curriculum vitae (CVs) of the principal investigators are provided in Appendix 16.1.4, and the folio of signatures is provided in Appendix 16.1.5.

7 INTRODUCTION

7.1 BACKGROUND

Dermatophytosis (tinea) is caused by dermatophytes belonging to the genera Trichophyton, Microsporum, and Epidermophyton. These fungi can invade keratinized tissues (skin, nail, hair) to establish infection. Their cell wall containing chitin/ glucosamine is water insoluble, which aids in the establishment of cutaneous infection. Clinically, tinea infections are classified according to the anatomical area involved.

- Tinea pedis is the infection of the feet including Athletes Foot and Moccasin Foot.
- Tinea capitis is infection of scalp hair.
- Tinea corporis is infection of the trunk and extremities and includes ring worm.
- Tinea manuum is infection of the hands,
- Tinea cruris is infection of the groin.
- Tinea barbae is infection of the beard area and neck.
- Tinea faciale is infection of the face.
- Tinea unguium (Onychomycosis) is infection of the nail. [1]

Fungal transmission occurs through direct contact with infected persons, animals, soil or fomites. Humid and moist skin predisposes to tinea infection; hence its occurrence is more common in tropical climates. [3]

Dermatophyte infections affect 1 of 3 Americans. The estimated lifetime risk of acquiring a dermatophyte infection is 10% to 20%. Tinea cruris presents in men more often than in women, with a gender disparity of 4:1. Other predisposing factors are tightly fitting clothing, summer months, climates with high humidity and moisture, obesity, and corticosteroid use. [2]

A classical presentation of tinea infection, known as "ringworm," is a lesion with central clearing surrounded by an advancing, red, scaly, elevated border representing inflammation. One or more lesions may appear. Inflammation assists in colonization and may result in vesicles on the border of the affected area. Atopic persons and those infected with zoophilic fungi tend to have more inflammation. [3]

The presentations of tinea infection are most commonly with pruritus, scaling and erythema, but can range from mild scaling to severe inflammation with bacterial superinfection. Tinea pedis may affect toe webs and plantar surfaces of one or both feet. It is characterized by toe-web scaling, fissuring, maceration, and erythema; in severe cases there may be pustules and bullae.

Typical symptoms of Onychomycosis (dermatophyte infection of the nails) include brittleness, change in nail shape, crumbling/roughness and or dystrophy of the nail, debris trapped under the nail, thickening/hardening of the nail and/or nail-bed (hyperkeratosis), separation of the nail from the nail-bed (onycholysis), discolouration of the nail

(leukonychia - white, yellow and/or brown) and loss of lustre/shine. The symptoms are largely cosmetic. However, in severe/long-term infections, the soft tissue around the nail may become inflamed and/or infected (including secondary bacterial infection which may be accompanied by suppuration) and the patient may suffer pain and partial loss of mobility; permanent damage to the nail and/or nail-bed can occur.

The diagnosis is made by presenting symptoms, clinical evaluation of the lesions. Definitive diagnosis is by demonstrating the fungal hyphae on microscopy by KOH preparation from scrapings obtained from the margin of the lesions, and fungal culture. Newer diagnostic methods include fungal Polymerase Chain Reaction (PCR) and identification of the fungus.

Treatment of dermatophyte infection involves primarily oral and/or topical formulations. They act by direct contact on the fungus, this type of action requires the simultaneous presence of antifungal and fungus for a minimum of time. [4] Topical antifungal agents are generally used for the treatment of superficial fungal infections. Oral formulations are useful when an extensive area is involved, or the infection is resistant to initial line of therapy.[5] Topical medications may be applied once or twice daily and are indicated primarily for tinea corporis/cruris, and tinea pedis/manuum. Use of oral antifungals may be practical where the tinea involvement is extensive or chronic, or where application of a topical agent is not feasible.[7]

Antifungals currently in use, therapeutically, fall under these broad categories: Allylamines (Terbinafine), Azoles (e.g. ketoconazole/ Miconazole), Antimetabolites (Flucytocine), Glucan synthesis inhibitors (Caspofungin), Polyenes (Amphoterecin-B/ topical Nystatin), and others (like Griseofulvin, ciclopirox, tolnaftate, undecylenate etc). Though currently, use of standard antifungal therapies can be limited because of toxicity, low efficacy rates, and drug resistance.[8] Patients often stop treatments when the skin appears healed, usually after about a week of treatment. If this short-term treatment is stopped, fungi recur more often when fungistatic, rather than fungicidal, drugs have been used. [6] Hence tinea infection continues to affect a significant population.

There is a significant demand for anti-fungal/anti-bacterial products for a variety of applications in the human heath, animal health and agriculture/horticulture sectors. According to the Antifungal Work Group at the National Institute of Health - USA, there is a "critical need for the development of antifungal agents". They also state that "there is not a single rapidly fungicidal, non toxic drug available".

To meet this demand, Biovite Australia Pty Ltd ("BIOVITE") has discovered an anti-microbial in a micro-organism which is a very early form of plant life ("Bioactive") named AMYCOT® that attacks and destroys fungi and some bacteria with no toxicity to humans. It also has been demonstrated to have skin repair properties; helping the healing process by accelerating the production of new skin, reducing inflammation, stopping itching, reducing some skin pigmentation, treating burns and bites. In a matter of two days or so, skin treated with the Bioactive regains a younger smoother appearance and texture. The Bioactive promotes rejuvenation of the skin as well as repair of skin damage.

Bioactive will be made available as an ingredient for a range of therapeutic products for anti-fungal/anti-bacterial applications for human, animal and horticultural use and for a wide range of cosmetic products for skincare. Formulations are being developed and tried for the treatment of Tinea, Acne, Eczema, Cradle Cap, Diaper Rash, Rosacea, Bites and Burns, Dermatitis, Scar Tissue Repair, Deep Nail Bed Infections, Dry and Aging-skin Care.

The Bioactive has significant advantages over existing anti-fungals in the areas of safety and efficacy. The Bioactive is 100% natural, harmless to all vertebrates and plants and it kills the fungi (a fungicide) rather than just treating the symptoms.

7.2 RATIONALE FOR STUDY

It is estimated that 30 to 40% of the population experience fungal diseases of the common varieties such as Tinea Infections (including Athlete's Foot, Jock Itch, and Ringworm etc.)

The market for treatments of fungal and bacterial diseases in humans is substantial. BIOVITE believes that the Bioactive is the first next-generation anti-fungal that is truly non-toxic and very efficacious. The Bioactive could provide an opportunity to expand existing market share with a more efficacious treatment for Tinea, or for companies that do not already have a product, the opportunity to enter this market with a next-generation natural-based product with demonstrably superior efficacy. The skin repair and rejuvenation properties of the Bioactive also offer major competitive advantages as an ingredient in the cosmetics and skin care market.

8 STUDY OBJECTIVES

Primary Objective:

To prove the efficacy of Biovite®'s Calmagen™ Dermaceutical cream & lotion as topical treatments for patients with Tinea (dermatophyte infection of the skin and/or hair follicles) and Onychomycosis (dermatophyte infection of the nails).

9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

This was a randomized, double blinded, placebo controlled, parallel-group, single center study designed to confirm the efficacy of Biovite®'s Calmagen™ Dermaceutical cream & lotion for topical application to the affected areas of skin in patients of either sex with severe to very severe presentations of Tinea.

The study was divided in three main phases:
(a) 1 to 15- days Screening Phase and Randomization

(b) Treatment Phase for Tinea (4 weeks) and Onychomycosis (12 weeks)
(c) Observation phase for Onychomycosis only (12 weeks)

The study population consisted of ambulatory human adult male and female patients with clinically proven severe presentations of Tinea who were randomized to receive either:
Treatment A: Biovite®'s Calmagen™ Dermaceutical cream or lotion for topical application to the affected areas of skin or nails.
Treatment B: Placebo cream or lotion for topical application to the affected areas of skin or nails.
A single centre in India participated in this study. A total of 28 eligible patients so as to include 10 Onychomycosis patients and 6 patients each of tinea cruris, corporis and pedis, were randomized into two groups in a 1:1 ratio.

Table 3: Treatment regimen

TREATMENT REGIMEN			
Total Patients (N)	**Study Treatment**	**Variable Treatment Duration**	**Dosing Regimen**
14	Treatment A	4 or 24 weeks	Biovite®'s Calmagen™ Dermaceutical cream or lotion for topical application to the affected areas of skin or nails and rubbed lightly as a thin smear to completely cover the affected area using finger twice daily (morning & evening) for 4 weeks or 12 weeks and once daily at night time for the additional 12 weeks (Onychomycosis subjects only).
14	Treatment B	4 or 24 weeks	Placebo cream or lotion for topical application to the affected areas of skin and rubbed lightly as a thin smear to completely cover the affected area using finger twice daily (morning & evening) for 4 weeks or 12 weeks and once daily at night time for the additional 12 weeks (Onychomycosis subjects only).

Once the written informed consent was signed, patient entered the study after which the screening and determination of eligibility phase of the study started. The patient was considered randomized upon receiving his randomized treatment assignment. The duration of the study varied from 4 to 24 weeks. During the Screening Phase, all patients came to the clinic for a screening visit, during which patient's eligibility was evaluated and screening assessments were performed. If the patient conforms to the eligibility criteria, baseline assessments were performed.

Eligible patients diagnosed with other types of Tinea except Onychomycosis were randomly assigned to receive Biovite®'s Calmagen™ Dermaceutical cream or Placebo cream at the initial visit (V1). Thereafter, patients returned to the clinic for at least 2 treatment visits to undergo study assessments, these visits (V2 toV5) were scheduled once in a week. Depending on the type of Tinea (other than Onychomycosis) the next visit at week 3 (V4) or 4 (V5) was planned. At end of study visit, further evaluation of the fungicide profile, treatment response and safety profile were performed.

Eligible patients diagnosed with Onychomycosis were randomly assigned to receive Biovite®'s Calmagen™ Dermaceutical lotion or Placebo lotion at the initial visit (V1). Thereafter, patients returned to the clinic for 3 treatment visits to receive the assigned treatment and undergo study assessments, these visits (V2, V3 & V4) were scheduled monthly. An optional telephonic assessment (V_{tel}) was performed as per the discretion of the principal investigator for compliance at Week-2 since start of treatment. Visit 4 (V4) after 3 months allowed further evaluation of the fungicide profile, treatment response of Biovite®'s Calmagen™ Dermaceutical lotion compared to Placebo lotion. An observation period of 3 months was carried out where at each month treatment response was assessed. During this phase patient applied the lotion once daily at night time.

A study flow chart is presented below:

Figure 1: Flow chart for Tinea patients (except Onychomycosis)

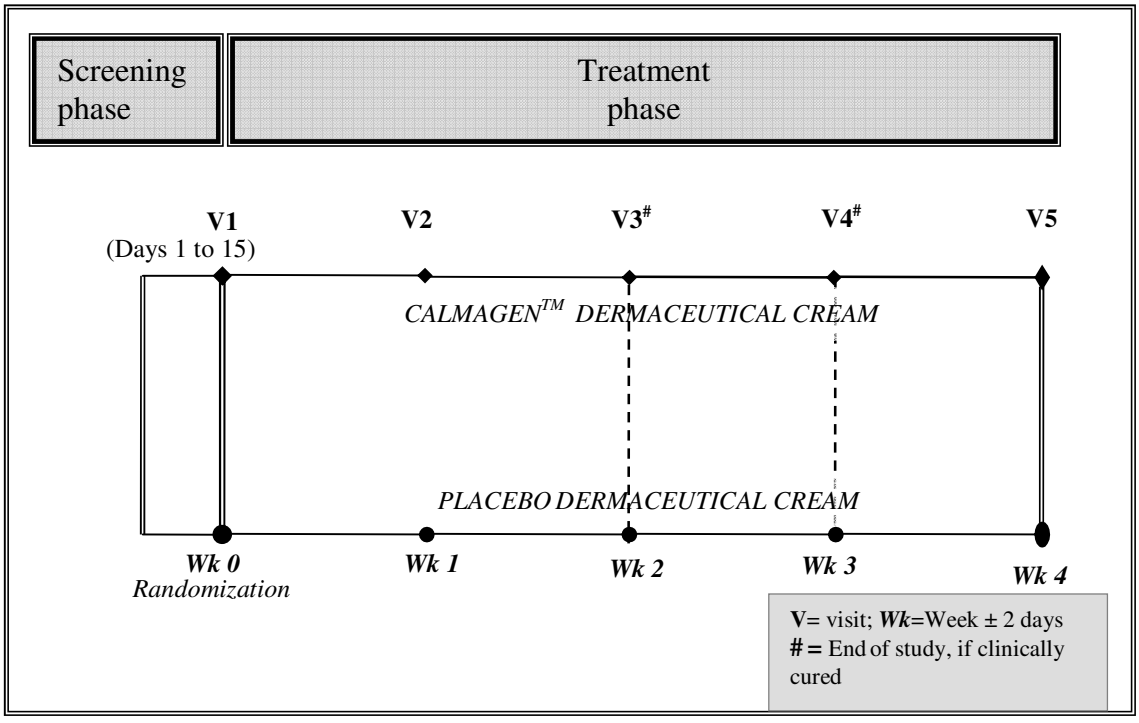


Figure 2: Flow chart for Onychomycosis patients

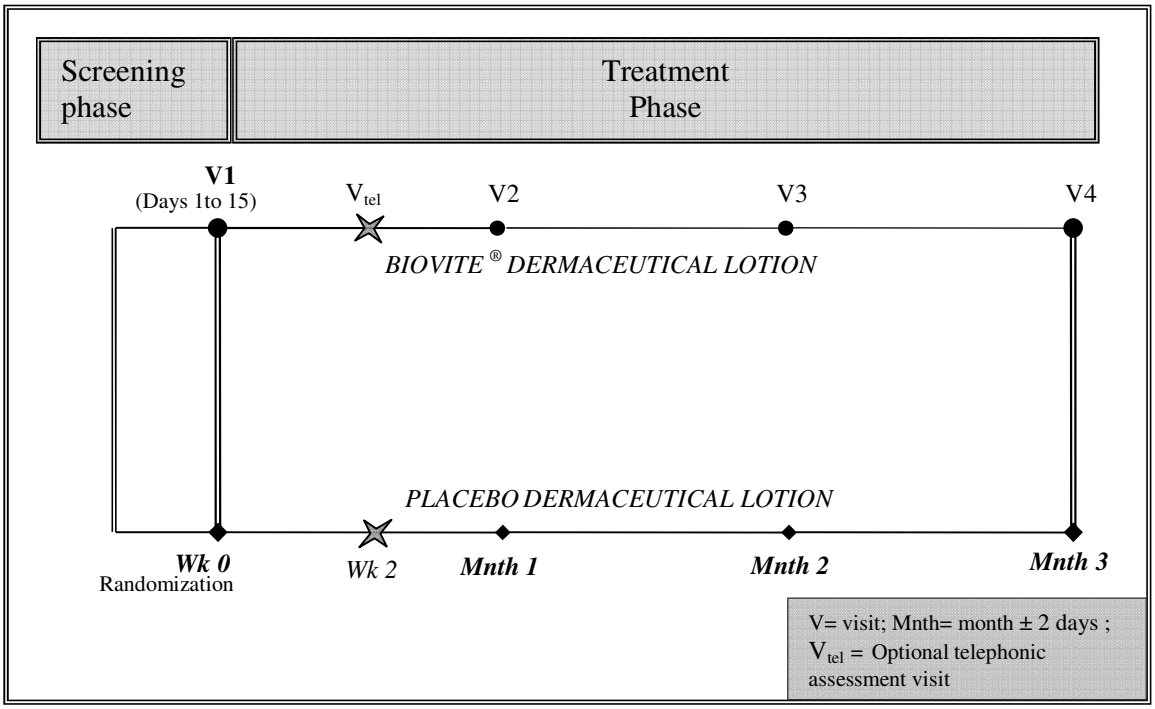


Table 4: Study events schedule (Tinea patients excluding Onychomycosis)

STUDY EVENTS SCHEDULE					
Visits	**Screening + Randomization**	**Treatment**			
	V1	**V2**	**V3#**	**V4#**	**V5**
		Week 1	**Week 2**	**Week 3◈**	**Week 4**
Tests and Assessments	**1 to 5 days**	**(±2 Day)**			
Informed consent	X				
Demographic data[1]	X				
Inclusion/exclusion criteria	X				
Medical History	X				
Concomitant Medication record	X	X	X	X	X
Signs and symptoms evaluation	X				
Physical Examination[2]	X				
Vital signs[3]	X	X	X	X	X
Confirmed diagnosis of Tinea	X				
Hematology[4]	X				
Biochemistry[5]	X				
Coagulation profile[6]	X				
Serology	X				
Urinalysis (routine & microscopy)[7]	X				

STUDY EVENTS SCHEDULE (contd.)					
Visits	**Screening + Randomization**	**Treatment**			
	V1	**V2**	**V3[#]**	**V4[#]**	**V5**
		Week 1	**Week 2**	**Week 3[◇]**	**Week 4**
Tests and Assessments	**1 to 5 days**	**(±2 Day)**			
Clinical evaluation of severity/size of tinea	X	X	X	X	X
Randomization	X				
Eligibility verification	X				
Tinea scrapings- KOH smear	X				X
Tinea scrapings – Fungal culture	X				X
Tinea scrapings – Live spore count	X				X
IP Accountability (dispensing) [8]	X	X	X	X	
IP Accountability (Used IP collection)[9]		X	X	X	X
Physician assessment of treatment response		X	X	X	X
Patient diary card dispensing [10]	X				
Patient diary card checking		X	X	X	X
Patient diary card collection [10]					X
Allergic testing	X				
Adverse Events	**Monitor and record throughout the study**				

X= Study activity applicable

Table 5: Study events schedule (Onychomycosis patients only)

STUDY EVENTS SCHEDULE					
Visit	**Screening + Randomization**	**Treatment**			
	V1	**V_{tel}**	**V2**	**V3**	**V4**
Tests and Assessments	**1 to 5 days**	**Week 2**	**Month 1**	**Month 2**	**Month 3**
		(±2 Days)			
Informed consent	X				
Demographic data[1]	X				
Inclusion/exclusion criteria	X				
Medical History	X				
Concomitant Medication record	X	X	X	X	X
Signs and symptoms evaluation	X				
Physical Examination[2]	X				
Vital signs[3]	X		X	X	X
Confirmed diagnosis of tinea	X				
Hematology[4]	X				
Biochemistry[5]	X				
Coagulation profile[6]	X				
Serology	X				
Urinalysis (routine & microscopy)[7]	X				

STUDY EVENTS SCHEDULE (contd.)					
Visit	**Screening + Randomization**	**Treatment**			
	V1	**V_{tel}**	**V2**	**V3**	**V4**
Tests and Assessments	**1 to 5 days**	**Week 2**	**Month 1**	**Month 2**	**Month 3**
		(±2 Days)			
Clinical evaluation of severity/extent of Onychomycosis	X		X	X	X
Randomization	X				
Eligibility verification	X				
Tinea scrapings- KOH smear	X				X
Tinea scrapings – Fungal culture	X				X
Tinea scrapings – Live Spore count	X				X
Telephonic compliance assessment		X			
IP Accountability (dispensing)[8]	X		X	X	
IP Accountability (Used IP collection)[9]			X	X	X
Physician assessment of treatment response			X	X	X
Patient diary card dispensing[10]	X		X	X	
Patient diary card checking			X	X	X
Patient diary card collection[10]			X	X	X
Allergic testing	X				
Adverse Events	**Monitor and record throughout the study**				

X= Study activity applicable

KEY:

1. Date of birth, gender, race, weight and height
2. General examination, head, ears, eyes, nose, throat, thyroid, cardiovascular, respiratory, abdomen, skin, neurological, extremities and back
3. Body temperature, heart rate and systolic/diastolic blood pressure measured in a sitting position after a 5-minute rest
4. Haematology: As per the tests listed in Appendix I of Protocol
5. Biochemistry: As per the tests listed in Appendix I of protocol
6. Coagulation: As per the tests listed in Appendix I of Protocol
7. Urinalysis: As per the tests listed in Appendix I of Protocol
8. IP/ Placebo was dispensed, if exhausted, to patients with specific instructions for application
9. Used IP/ Placebo was collected if container is empty/ likely to be so before next visit, from patients and new IP/Placebo dispensed.
10. To be dispensed, if previously dispensed card was completed; If previously dispensed diary card was completed, was collected from patient.
The V5 Assessment schedule was followed if this was the last visit (end of study) for any individual in the study, as per PI assessment
◈ If this visit was not required, the end of study visit could been performed at Week 4 after week 2

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

The double blinded, placebo controlled, parallel-group randomized study design was chosen as appropriate considering the clinical treatment methodology and to achieve the objectives of the study . This was a comparative study to assess the fungicidal profile, efficacy and safety of the study treatment. The study was conducted as a clinical trial and with accordance to the guidelines set by Independent Ethics Committee (IEC), Schedule Y of the Indian Drugs and Cosmetics Act, 1940, and ICH - GCP.

The twice daily topical application of Biovite®'s Calmagen™ Dermaceutical cream & lotion for the determined treatment period was expected to provide adequate treatment.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

To be eligible for entry in this study, patient must:

1. Be a male or female ≥ 18 years of age
2. Be diagnosed by the Principal Investigator or designee as suffering from Tinea of combined severity (itching, erythema and scaling) score of 8 or more as in appendix 3 or severe grade of onychomycosis as in appendix 4 of protocol
3. Subjects with positive KOH and positive fungal culture test along with identification of the dermatophyte and presence of live spores.
4. Understand and conform to the procedures involved in and agree to participate in the study by giving informed, written consent.
5. Be able to give consent for taking photographs of the affected region before, during and after the study period.

9.3.2 Exclusion Criteria

To be eligible for entry in this study, patient must not:

1. Have had used any oral or topical Tinea treatments, within one week prior to the screening assessment.
2. Have had ingested any drug in the week prior to the start of treatment or during the treatment period, which, in the opinion of the Principal Investigator, could compromise the study (Note: Oral, injectable or implant contraceptive for female volunteers is acceptable).
3. Have had any history of allergy or intolerance to any drug, which in the opinion of the principal investigator poses a risk to the patient
4. Be pregnant or breast-feeding females.
5. Have had received an investigational drug or participated in a clinical trial within the last 30 days

6. Have had any clinically serious and/or unstable intercurrent infection, medical illnesses or conditions that are uncontrolled or whose control, in the opinion of the Principal Investigator, may be jeopardized by participation in this study or by the complications of this therapy
7. Have had any Hypersensitivity to Biovite® dermaceutical formulation (cream & lotion)
8. Patient with a positive test for hepatitis B, C, and who is positive or reactive for antibodies to HIV 1 and 2.

9.3.3 Removal of patients from therapy or Assessment

Criteria for discontinuation:

The PI or Sponsor could discontinue individual patients from the study at any time. Patients were encouraged to complete the study. However, they might voluntarily withdrew at any time. If a patient discontinued, the PI would provide a written report on the appropriate CRF page describing the reason for discontinuation. If a patient withdrew or was discontinued from the study before completion, every effort was made to complete the last scheduled assessments. Dropouts were replaced with suitable alternative patients.

Patients could be removed from the study for the following medical or administrative reasons:

- AE or abnormal laboratory value

If a patient suffered an AE or had an abnormal laboratory value that in the judgement of the PI, or the Sponsor presented or suggested an unacceptable consequence or risk to the patient, the patient was discontinued from further participation in the study. The PI could follow the patient until satisfactory resolution of the AE.

- Intercurrent illness

A patient was also been discontinued from the study if, in the judgement of the PI, the patient developed an intercurrent illness or complication that was not consistent with the protocol requirements or that in any way justified the patient's withdrawal from the study.

- Administrative discontinuation

After consultation between the PI and the Sponsor, a patient could had been discontinued from the study for the following administrative reasons:

- Voluntary withdrawal
- Non compliance or failure to comply with protocol requirements (All occurrences of noncompliance would be documented on the appropriate pages of the CRF)
- Refusal of study drug administration
- If, for any reason, the patient refused study drug administration during the study, the patient was discontinued, and the reasons for refusal would had been documented on

the appropriate page of the CRF. When possible, efforts were made to monitor the patient for AEs and to complete the last scheduled assessments following such discontinuation. These efforts were documented on the appropriate page of the CRF.

The final report included reasons for withdrawal.

9.4 TREATMENTS

9.4.1 Treatments Administered

All randomized patients applied Biovite®'s Calmagen™ Dermaceutical formulation or placebo formulation topically to the affected skin or nail twice daily (morning & evening) or once daily at night (Onychomycosis patients only during the additional 3 months observation period).

Table 6: Treatment regimen

TREATMENT REGIMEN			
Total Patients (N)	**Study Treatment**	**Variable Treatment Duration**	**Dosing Regimen**
14	Treatment A	4 or 24 weeks	Biovite®'s Calmagen™ Dermaceutical cream or lotion for topical application to the affected areas of skin or nails and rubbed lightly as a thin smear to completely cover the affected area using finger twice daily (morning & evening) for 4 weeks or 12 weeks and once daily at night time for the additional 12 weeks (Onychomycosis subjects only).
14	Treatment B	4 or 24weeks	Placebo cream or lotion for topical application to the affected areas of skin and rubbed lightly as a thin smear to completely cover the affected area using finger twice daily (morning & evening) for 4 weeks or 12 weeks and once daily at night time for the additional 12 weeks (Onychomycosis subjects only).

Patients were instructed to topically apply Biovite®'s Calmagen™ Dermaceutical Cream/Lotion formulation or Placebo formulation to the affected skin or nails rubbed lightly in as a thin smear to completely cover the affected area in the case of the Cream on Tinea skin infections and in the case of Onychomycosis over the face of the nail, behind the nail from the top and around the margins and cuticle where the nail meets the skin and allowed it to soak well into the area using finger twice daily (morning &

evening) for the pre-determined treatment period. The patients washed their hands before and after application.

9.4.2 Identity of Investigational Product

Biovite Australia Pty Ltd, ("Biovite") supplied the investigational products used in the study. Drugs were manufactured complying with all required regulations and sufficient quantities were supplied to the clinical study facility by the sponsor.

Table 7: Investigational Product Details

Product	**Test**		**Reference**	
Active Ingredient	Amycot		Placebo	
Dosing Regimen	Twice Daily		Twice Daily	
Manufacturer	**Biovite Australia Pty Ltd, ("Biovite")** Unit1, Enterprise Plaza 45 Township Drive West Burleigh, Queensland 4219, Australia		**Biovite Australia Pty Ltd, ("Biovite")** Unit1, Enterprise Plaza 45 Township Drive West Burleigh, Queensland 4219, Australia	
Dosage Form	Cream	Lotion	Cream	Lotion
Batch/Lot No.	B9566	B9744	B08529	B08528
Treatment ID	A	C	B	D
Manufacture Date	NA	NA	NA	NA
Expiration Date	09/2011	02/2012	09/2010	11/2011
The study medication was stored in a locked area with limited access under room temperature conditions and protected from light and moisture.				

9.4.3 Method of assigning patients to treatment group

The patients were assigned to either treatment or placebo arm in accordance with the computer-generated randomization schedule (in suitable blocks) and stratified by site. A random number was allocated to each box of study medication, and the sites dispensed study medication in sequential order as the patients qualify for participation in the study. MAL kept one set of sealed envelopes containing the treatment codes while a second set kept at the participating sites with the corresponding study medication. Upon completion of the study, all sealed envelopes were returned to the MAL

9.4.4 Selection of doses in the study

The dose selected in this study was twice daily topical application of Biovite®'s Calmagen™ Dermaceutical formulation and Placebo formulation to the affected skin or nails rubbed lightly in as a thin smear to completely cover the affected area.

9.4.5 Timing of dose of each patient

All patients were instructed to apply the study medication twice daily, Morning and Evening).

9.4.6 Blinding

All patient, investigators, site and sponsor personnel involved in conducting the study were blinded to treatment codes until the database was locked.

9.4.7 Prior and Concomitant Therapy

Medications and/or therapies other than the IP for the treatment of Tinea/Onychomycosis were brought to the notice of PI during the study and were recorded into the patient's diary and CRF in detail.

Permitted concomitant medications

Permitted concomitant treatments included all over the counter, prescribed and any herbal medications for conditions not listed under inclusion / exclusion criteria.

Prohibited concomitant medications

Any oral or topical Tinea treatments within one week prior to screening and throughout the course of study were prohibited. Ingestion of any other drugs within one week prior to screening that the Principal Investigator or designee believed could compromise the safety of the subject or the study outcomes.

Patients were instructed to report to the investigator any medication used over the course of the study. The principal investigator addressed the significance of the reported medication used on study integrity. At the discretion of the investigator, these patients continued study participation if the medication was not anticipated to alter study integrity.

9.4.8 Treatment Compliance

IP was dispensed by the Principal Investigator or under his supervision by his authorized designee at the scheduled visits. Participants required to return the dermaceutical cream/lotion at each scheduled visit to the clinic. The unused dermaceutical cream/lotion was reconciled at each scheduled visit and used to determine drug compliance. This was recorded in the patient's diary and CRF.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy and Safety Measurements Assessed

9.5.1.1 Mycological assessment

Mycological cure assessed by negative KOH preparation, fungal culture, and reduction in live spore counts at the end of study.

Tinea Scrapings

Patients were required to give Tinea scrapings at screening/randomization and at last treatment visit (at *week 4, V5 of treatment visit for all patients diagnosed with other types of Tinea except Onychomycosis; at month 3, V4 of treatment visit for all patients diagnosed with Onychomycosis)* for KOH preparation, fungal culture for identification by pathology of the fungi and live spore counts.

The KOH preparations, Fungal Cultures and live spore counts were performed as per the standardized procedure available. The sample collection and transport as well as the procedure for performing live spore count were as per the standardized validated method available presently.

9.5.1.2 Clinical Assessment of the Size and Severity of Tinea, Extent and severity of Onychomycosis

Patients returned to the study centre during the predetermined treatment period and as per their scheduled visits for clinical assessment of the size and severity of Tinea.

A 'Target Lesion' is a lesion which clinically represents Tinea infection occurring in the corresponding anatomical location, bearing the classical symptom(s) of Tinea fungal infection.

A target lesion was identified by the PI at randomization, for the purpose of efficacy assessment and the study parameters was applied to the same as mentioned in the protocol.

Clinical assessment

The size# and severity of the patient's Tinea was compared to the size and severity at the start of the study and at every scheduled assessment visits.
Reduction in the size of the area affected:
This was scored such as
100%-cleared
90-99%-excellent
50-89%-good
25-49%-fair
<24%-poor
Increase in size-worse

Severity or intensity / density of infection (Tinea other than Onychomycosis):
This was scored individually for itching, erythema and scaling:
0-absent
1-mild
2-moderate
3-severe
4-very severe
Reduction in combined severity score:
This was scored such as

100%-cleared
90-99%-excellent
50-89%-good
25-49%-fair
<24%-poor
Increase in severity-worse

#Measured in cm either in length or in breadth for a given lesion. The lesion was measured by the same study personnel at the same measuring points for that given lesion in subsequent assessment visits

Refer appendix II and III of protocol for scoring scale

Additionally, based on the article by A.Y.Sergeev, A.K.Gupta et.al. and key clinicians' expertise, a scale was used here which was used for assessing the initial condition and the changes during treatment of fungal nail (Onychomycosis).

Reduction in the nail plate % involvement
This was scored such as
>75%-very good response
50-74%-good
25-49%-fair
<24%-poor
Increase in extent-worse

Severity or intensity / density of infection Onychomycosis):
This was scored such as:
0-absent
1-mild
2-moderate
3-severe

Reduction in severity score:
This was scored such as
>75%- very good response
50-74%-good
25-49%-fair
<24%-poor
Increase in severity-worse

Refer appendix IV of protocol for extent and severity score of Onychomycosis

9.5.1.3 Response to Treatment

The response to treatment was scored by the Principal Investigator (Appendix II) at clinic visits, by mycological assessment, by clinical assessment and daily by the patients in their diary cards, as follows:

Response to treatment	*Score*
Worse	-1
No Change	0
Slight improvement	1
Moderate improvement	2
Great improvement	3
Cure	4

On the basis of this assessment, the patient's response to treatment was scored by the Principal Investigator or designee for assessment of clinical response as per Appendix II Patients similarly scored their own response to treatment daily, in their diary cards.

9.5.1.4 Photographs

The photographs of the Tinea served as a record of the clinical assessment and repair of physical damage caused by the fungal infection. It also served as a record of the progress from the first assessment to subsequent assessments.

The photographs were taken in close up mode at a minimum image resolution of 3008 x 2000 pixels or 6.1 mega pixels in .JPEG format. Photograph was taken in such a way so that the subject identity was not established. The concerned photograph was appropriately labeled with the respective unique patient identity code (PIC)/ Randomization ID, subject initials and date on which it was taken.

9.5.1.5 Adverse events:

AE(s) were monitored using the solicited checklist, as volunteered by the patient, by specific questioning, by review of the patient's study diary and, as appropriate, by examination by the investigator and was categorized descriptively. The total number of AE(s) based on their frequency, causality, as well as severity was compared between treatment and control arms. These events were summarized and reported as appropriate.

Any AE recorded after screening prior to the use of the study medication was considered as pre-treatment AE, while those AEs recorded after the first dose of study medication till the end of treatment were considered as post-treatment AE(s). The severity of AE(s) was

categorized by the investigator as mild, moderate, severe and very severe, while the relationship was described unrelated, unlikely, possibly, probably, definitely related to the study medication. The frequency and severity of the AE profiles for each treatment was evaluated. Patients recorded the occurrence of any AE in the diaries provided to them.

9.5.1.6 Assessment of vital signs:

The PI or nurse measured the following vital signs: oral temperature, blood pressure, pulse rate and respiratory rate. Such examination was done on screening, and on all scheduled visits. The actual time of measurement was recorded in the CRF.

Assessment of the vital signs was done, if the attending physician finds it necessary at any time during the conduct of the study and the same was recorded in the CRF with reasoning. In case of any abnormality in vital signs before dosing, medical opinion was taken as to whether to dose the patient or not.

9.5.2 Appropriateness of Variables

The variables measured in this study were standard variables for clinical studies for treatment of severe to very severe Tinea.

9.5.3 Efficacy Variables

9.5.3.1 Primary Efficacy Variables

- Mycological cure assessed by negative KOH preparation, fungal culture, and reduction in live spore counts at the end of study.

9.5.3.2 Secondary Efficacy Variables

Efficacy end-point:

- Reduction in size and severity score of Target lesion (size and severity score of Tinea) since baseline, assessed at the end of study. Reduction in extent and severity score of Target lesion (extent & severity score of Onychomycosis) since baseline, assessed at the end of study.
- Clinical cure defined as Investigator global assessment response of 'cleared' or 'excellent'.
- Improvement in lesions assessed by photographic record at baseline and at end of study.

9.5.4 Drug Concentration Measurements

The study did not include any drug concentration measurements.

9.6 DATA QUALITY ASSURANCE

Monitoring and Training:

Site selection visits were made by the Clinical Research Associates (CRAs) of MAL. During site initiation, the investigator and the staff at the study site were trained on protocol, ICF procedure, ICH GCP guidelines, randomization procedure, AE and SAE reporting, source documentation and CRF filling, maintenance of the investigator site file, clinical supplies dispensing & accountability and storage procedures. During the study, the CRA had regular contact with the study site. These contacts included visits to confirm that facilities remained acceptable, that the site personnel adhered to the protocol, that data was accurately recorded in the CRFs and to provide information and support to the investigator. The CRA ensured that the regular updating of the inventory and maintenance of IP dispensing log for the individual patient, regular temperature control by maintaining temperature log, etc. which were required for drug accountability. Source data verification (a comparison of the data in the CRF with the hospital records and other records at the study site) was also done.

All clinical studies conducted by MAL were subject to quality control and quality assurance measures as dictated by the appropriate department's operational documents like SOP's and process documents. The quality assurance activities were conducted by quality assurance personnel who after reviewing the data and the report declared the quality of the conduct of the study. Refer Appendix 16.1.8 for QA statement.

Audit

There was no site audit done for this study.

Data Management

Double Data entry, data validation and error rate calculation were done by Data Management and biostatistics personal at Manipal Acunova. The error rate for critical data was 0% and non-critical data was 0.02%. The data management personnel raised queries for discrepancies that required further clarification from the site and also for missing data using the "Data Clarification Form". Resolution of data discrepancies was completed before the database was locked.

Dictionaries and coding terminology

AEs and Medications were not coded.

9.7 STATISTICAL METHODS PLANNED AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical Plans

A comprehensive Statistical Analysis Plan (SAP) Version 1.0 dated 25 Feb 2011 was prepared and signed off prior to performing the statistical analysis and prior to unblinding. A copy of SAP is provided in Appendix 16.1.9. A summary description of the statistical analysis is provided below.

9.7.1.1 Patients Included in the analysis

All patients who received study drug and had at least one efficacy measurement subsequent to the baseline visit was included in the Modified Intention-to-Treat (MITT) population, the MITT population was the primary population for the efficacy analysis. Patients who completed both the baseline visit and end of treatment visit and who had no major protocol violations were included in the Per-Protocol (PP) population; the PP population was the secondary population for the efficacy analysis.

Modified Intention-to-treat population:
All randomized patients who received study medication and had at least one efficacy measurements were included in the MITT population.

Per-Protocol population:
All randomized patients who completed both baseline and the end of treatment visit and who had no major protocol violations were included in the PP population.

Safety population:
For safety evaluation, all patients randomized and dispensed study medication were included in the safety population. For analysis of the overall tolerance score, 3 populations were analyzed due to missing data, 1) subjects with data, 2) impute missing with failure, 3) impute missing with success. Since no imputation was done for missing local tolerance data, the analysis population only included subjects with data and did not include the entire safety population.

9.7.1.2 General Considerations

Statistical analyses were performed after all patients had ended their participation in the study and the database was locked.

The SAS® package (SAS® Institute Inc., USA, and Version 9.2) was used for statistical evaluation.

9.7.1.3 Demographic and Baseline Characteristics

The following demographic and baseline characteristics were summarized by treatment group as follows: age, height, weight, gender, race, and vital signs

- For continuous measurements such as age, the mean, median, standard deviation and range were tabulated.
- For categorical measurements such as gender, the frequencies were computed.

9.7.1.4 Analysis of Efficacy

The following analyses were performed.

Analysis primary efficacy endpoint:

- Percentage of patients achieving mycological cure since baseline, at the end of the study.

Analysis of secondary efficacy endpoints:

Efficacy end-point:

- Reduction in size and severity score of Target lesion (size and severity score of Tinea) since baseline, assessed at the end of study. Reduction in extent and severity score of Target lesion (extent & severity score of Onychomycosis) since baseline, assessed at the end of study
- Clinical cure defined as Investigator global assessment response of 'cleared' or 'excellent'.
- Improvement in lesions assessed by photographic record at baseline and at end of study.

9.7.1.5 Analysis of Safety and tolerability

Analysis of safety endpoints:

Safety analysis was analyzed for the safety population. Biovite® Calmagen™ Dermaceutical formulation (cream & lotion) safety profile were assessed on the basis of the following assessments:

For adverse events, the number and the proportion of patients who experienced AEs were computed by treatment group. The number and percentage of patients with post treatment AEs during treatment were summarized for each treatment group. AEs were also summarized by severity (mild, moderate, severe) and by relationship to study medication (not related, unlikely, possibly, probably, definitely) in a similar way.

Proportion of patients who used concomitant medication during the study period were computed for each treatment group.

Vital signs were recorded at every study visit. Descriptive statistics such as mean, standard deviation, median, minimum and maximum values were provided for each study visit and also on the change from visit 1(V1) to study end visit.

9.7.2 Handling of Drop-outs and Missing Data

Patients who did not complete the study for at least Week 2 (V3) for patients diagnosed with other types of Tinea except Onychomycosis and Month 3 (V4) for patients diagnosed with Onychomycosis, were considered dropouts and all the dropouts were replaced with suitable alternative patients.

9.7.3 Determination of Sample Size

The sample size for this study was computed based on the reference study by Jerajani et al (2000). The global evaluation response of the clinical condition compared to baseline was reported as 'cleared' or 'excellent' in 81% of the patients in the reference study. Assuming a similar response in the test group and a 10% response of cleared or excellent in the placebo group in the present study, there was over 95% power to detect a significant difference between the 2 groups with 14 subjects per group (28 subjects overall) at the 5% level of significance, and assuming a 20% dropout rate.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.8.1 Changes in the study conduct

There were no changes in the study conduct.

9.8.2 Changes in the planned analysis

There were no changes in the planned analysis.

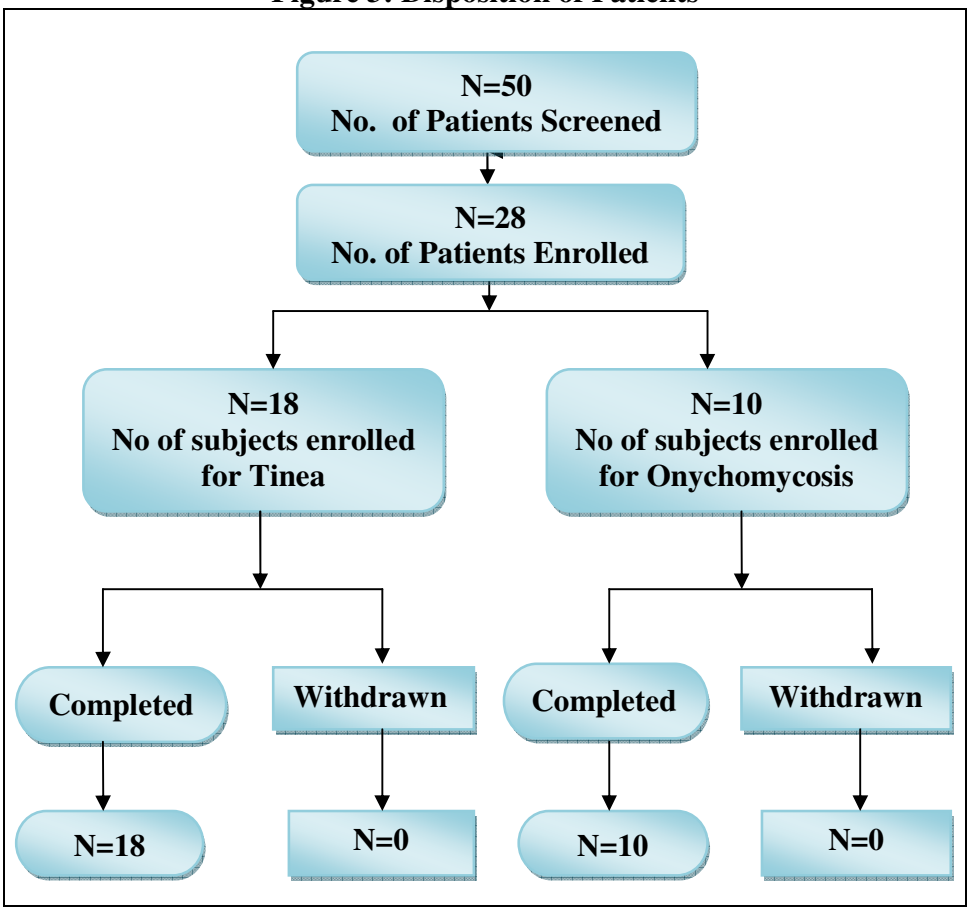
10 STUDY PATIENTS

10.1 DISPOSITION OF PATIENTS

A single center recruited 28 patients for this study. All 28 patients completed the study & none of them withdrew from the study. The first patient was enrolled on 27 Mar 2010 & the last patient completed the study on 29 Jan 2011.

Number of patients enrolled, completed, withdrawn and reasons for withdrawal are provided in Figure 3.

Figure 3: Disposition of Patients



10.2 PROTOCOL DEVIATIONS

No major protocol deviations occurred during the conduct of the study. However there were 14 minor deviations reported during the study which were acceptable. Most of the deviations belonged to the release of the fungal culture report which got extended by 1 or

2 days. Other deviations reported were in taking the scrapings for Tinea after the visit window period.

11 EFFICACY EVALUATION

11.1 DATA SETS ANALYSED

Two populations were considered for the analysis: Per protocol (PP) population and Modified intention to treat (MITT) population. All the efficacy analyses were carried out for both populations of which MITT population was considered as primary and PP population was considered as secondary.

A total of 28 (100.0%) patients were included under MITT population of which 18 patients belonged to Tinea and another 10 patients for Onychomycosis. Same number of patients was included under PP population as there were no withdrawals in this study. Further details on number of patients included under MITT and PP population are provided in Table 8**Error! Reference source not found.**.

Individual summary of number of subjects included and excluded from Safety, MITT and PP analyses with reasons for exclusion of Tinea and Onychomycosis patients are provided in (Post Text Table 1 and Post Text Table 2) section 14.1.

Table 8: Number of subjects included and excluded from Safety, MITT and PP analyses with reasons for exclusion of Tinea and Onychomycosis subjects

Subject Status	Test (N=14)		Placebo (N=14)		ALL (N=28)	
	n	%	n	%	n	%
Number of subjects enrolled	14	100.0	14	100.0	28	100.0
Included in the Modified-Intention-to-treat analysis	14	100.0	14	100.0	28	100.0
Included in the Per-Protocol analysis	14	100.0	14	100.0	28	100.0
Excluded from the Per-Protocol analysis	0	0.0	0	0.0	0	0.0
Included in the Safety analysis	14	100.0	14	100.0	28	100.0

Test= Biovite Dermaceutical formulation (cream & lotion)
Placebo= Placebo formulation (cream & lotion)
* Same subject could be excluded due to more than one reason
Source Listing: Randomization, Inclusion/Exclusion, End of study

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The treatment groups were comparable with respect to the demographic characteristics measured at baseline. Table 9 and Table 10 represent the summary of patient baseline characteristics (gender, race, age, height and weight) for the MITT population. All the patients were Asians. Study population included a total of 8 (28.6%) females and 20 (71.4%) males. The age of the patients ranged from 20.0 to 67.1 years with a mean (SD) of 41.5 (11.58) years. The height of the patients ranged from 152.0 to 174.0 cms with a

mean (SD) of 166.8 (6.40) cms. The weight of the patients ranged from 49.0 to 82.0kgs with a mean (SD) of 65.6kgs (9.11). Individual summary of patient demographic characteristics at screening, categorical variables of Tinea and Onychomycosis (MITT) is provided in (Post Text Table 5 to Post Text Table 8) section 14.1.

Table 9: Summary of patient demographic characteristics at screening: categorical variables of Tinea and Onychomycosis (Modified-Intention-to-treat Population)

Variable	Categories	Test (N=14)		Placebo (N=14)		ALL (N=28)	
		n	%	n	%	n	%
Gender	Female	5	35.7	3	21.4	8	28.6
	Male	9	64.3	11	78.6	20	71.4
Race	Asian	14	100.0	14	100.0	28	100.0

Test= Biovite® Dermaceutical formulation (Cream)
Placebo= Placebo formulation (Cream)
n/%= Number/Percentage of subjects with the given characteristics
Source listing: Demography.

Table 10: Summary of subject demographic characteristics at screening: continuous variables of Tinea and Onychomycosis (Modified-Intention-to-treat Population)

Variable	Categories	Test	Placebo	ALL
Age(in years)	N	14	14	28
	Mean	37.2	45.8	41.5
	SD	9.40	12.26	11.58
	Median	39.2	47.9	40.7
	Min	22.7	20.0	20.0
	Max	51.6	67.1	67.1
Height(cm)	N	14	14	28
	Mean	165.2	168.4	166.8
	SD	7.06	5.45	6.40
	Median	167.0	170.0	168.5
	Min	152.0	157.0	152.0
	Max	174.0	174.0	174.0
Weight(kg)	N	14	14	28
	Mean	63.3	68.0	65.6
	SD	8.59	9.32	9.11
	Median	61.0	70.0	67.5
	Min	50.0	49.0	49.0
	Max	76.0	82.0	82.0

N = Number of subjects with non-missing values
Test= Biovite® Dermaceutical formulation (Cream)
Placebo= Placebo formulation (Cream)
Source listing: Demography.

11.3 EFFICACY RESULTS AND TABULATION OF DATA

11.3.1 Analysis of Efficacy

11.3.1.1 KOH smear

Table 11 represents the summary of KOH smear by visit for patients with Tinea and Onychomycosis in MITT population. At the screening visit, 28 (100%) patients with Tinea and Onychomycosis were positive for KOH smear in both the test & placebo group. However at the end of the study visit, 13 (92.86%) patients were found negative in the test group & in the placebo group, all 14 (100.00%) of the patients remained positive.

Individual summary of KOH smear by visit for patients with Tinea and Onychomycosis (MITT) is given in the (Post Text Table 10 and

Post Text Table 11) section 14.2.

Table 11: Summary of KOH smear by visit for patients with Tinea and Onychomycosis (Modified Intention to treat Population)

VISIT	Test (N=14)				Placebo (N=14)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	14	100.00	0	0.00	14	100.00	0	0.00
End of study	1	7.14	13	92.86	14	100.00	0	0.00

End of study = visit 5
Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/% = Number/percentage of patients with the Tinea scrapings test done
Source Listing: Tinea scrapings

Table 12 represents the analysis of percentage of patients achieving mycological cure from baseline at end of the study as assessed by KOH smear for subjects with Tinea and Onychomycosis in MITT population. At the end of the study, the mycological cure was achieved in 13 (92.9%) out of 14 patients in the test group (CI; 79.4, 100.0) and none of the 14 patients in the placebo group achieved mycological cure. It showed significance with a p-value of <0.001 when the test group was compared with the placebo group.

Individual analysis of percentage of patients achieving mycological cure from baseline at end of the study as assessed by KOH smear for subjects with Tinea and Onychomycosis in MITT population is provided in the (Post Text Table 15 and Post Text Table 17) Section 14.2. Individual analysis also showed significance for the test group with a p-value of 0.0004 and 0.0079 for Tinea and Onychomycosis respectively.

Table 12: Analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by KOH smear for subjects with Tinea and Onychomycosis (Modified Intention to treat Population)

Treatment	KOH smear			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	14	0 (0 %)	0 (0 %)	0 (0 %)	(0.0 ,0.0)	<.0001
Test	14	0 (0 %)	13 (92.9 %)	13 (92.9 %)	(79.4 ,100.0)	

- End of study for the patients with Tinea is considered as visit 5 and patients with Onychomycosis is considered as visit 4
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n = Number of subjects with the Tinea scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

11.3.1.2 Fungal culture

The summary of fungal culture by visit for patients with Tinea and Onychomycosis in MITT population is provided in Table 13. The test & the placebo group patients with Tinea and Onychomycosis were 100% positive at the screening visit for the fungal culture. While at the end of the study, all 14 (100.00%) patients in the test group were found negative and in the placebo group 8 (57.14%) patients were found positive.

Individual summary of fungal culture by visit for patients with Tinea and Onychomycosis in MITT population is provided in (Post Text Table 20 and Post Text Table 22) section 14.2

Table 13: Summary of Fungal culture by visit for patients with Tinea and Onychomycosis (Modified Intention to treat Population)

VISIT	Test (N=14)				Placebo (N=14)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	14	100.00	0	0.00	14	100.00	0	0.00
End of study	0	0.00	14	100.00	8	57.14	6	42.86

Test=Biovite® Dermaceutical formulation (Cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects with Tinea
Source Listing: Tinea scrapings

Table 14 represents analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by fungal culture for subjects with Tinea and Onychomycosis in MITT population. At the end of the study, all the 14 (100%) patients in the test group achieved mycological cure (CI; 100.0, 100.0) whereas in the placebo group 6 (42.9%) of the 14 patients achieved mycological cure (CI; 17.0, 100.0), as assessed by the fungal culture with a significant p-value of 0.0019.

Individual analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by Fungal culture for subjects with Tinea and Onychomycosis in MITT is provided in the (Post Text Table 25 and Post Text Table 27) section 14.2. Individual analysis showed significance in the test group for Tinea (p=0.0294) and didn't show significance for Onychomycosis (p=0.1667).

Table 14: Analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by Fungal culture for subjects with Tinea and Onychomycosis (Modified Intention to treat Population)

Treatment	Fungal culture			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	14	0 (0 %)	6 (42.9 %)	6 (42.9 %)	(17.0 ,100.0)	0.0019
Test	14	0 (0 %)	14 (100 %)	14 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Tinea is considered as visit 5 and patients with Onychomycosis is considered as visit 4
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n = Number of subjects with the Tinea scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

11.3.1.3 Spore count

Table 15 summarizes the spore counts by visit for patients with Tinea and Onychomycosis in MITT population. All the patients belonging to test & the placebo group with Tinea and Onychomycosis showed positivity for live spore count at the screening visit. While at the end of the study visit, all the 14 patients (100.00%) of test group showed no spore count and in the placebo group 8 (57.14%) of the patients showed positivity for live spore count.

Individual summary of spore counts by visit for patients with Tinea and Onychomycosis in MITT population is provided (Post Text Table 30 and Post Text Table 33) in the section 14.2.

Table 15: Summary of Spore counts by visit for patients with Tinea and Onychomycosis (Modified Intention to treat Population)

VISIT	Test (N=14)				Placebo (N=14)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	14	100.00	0	0.00	14	100.00	0	0.00
End of study	0	0.00	14	100.00	8	57.14	6	42.86

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of patients with Tinea
Source Listing: Tinea scrapings

Table 16 represents the analysis of percentage of patients achieving mycological cure from baseline at end of study as assessed by spore counts for patients with Tinea and Onychomycosis in MITT population. At the end of the study, all the 14 (100%) patients in the test group achieved mycological cure (CI; 100.0, 100.0) whereas in the placebo group 6 (42.9%) of the 14 patients achieved mycological cure (CI; 17.0, 100.0), as assessed by the spore counts with a significant p-value of 0.0019.

Individual analysis of percentage of patients achieving mycological cure from baseline at end of study as assessed by spore counts for patients with Tinea and Onychomycosis in MITT population is provided in the (Post Text Table 35 and Post Text Table 37) section 14.2. Individual analysis showed significance in the test group for Tinea (p=0.0294) and didn't show significance for Onychomycosis (p=0.1667).

Table 16: Analysis of percentage of patients achieving mycological cure from baseline at end of study as assessed by Spore counts for patients with Tinea and Onychomycosis (Modified Intention to treat Population)

Treatment	Fungal culture			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	14	0 (0 %)	6 (42.9 %)	6 (42.9 %)	(17.0 ,100.0)	0.0019
Test	14	0 (0 %)	14 (100 %)	14 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Tinea is considered as visit 5 and patients with Onychomycosis is considered as visit 4
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n/p = Number/proportion of patients with the Tinea/Onychomycosis scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Fungal Identification Results

Table 17 and Table 18 summarizes the different species of fungus and fungal culture results in Tinea and Onychomycosis patients respectively. At baseline, in the test group of Tinea patients, the fungal culture was positive in all 9 patients and organism isolated was Epidermophyton floccosum in 6 patients, Trichophyton rubrum in 2 patients and Trichophyton violeoceum in one patient. While at the end of the study, fungal culture was negative for all the patients identified to be positive at the baseline.

At baseline, in the placebo group of Tinea patients, the fungal culture was positive in all 9 patients and organism isolated was Epidermophyton floccosum in 5 patients, Trichophyton rubrum in 2 patients and Trichophyton violeoceum in 2 patients. While at the end of the study, fungal culture was negative for 3 patients out of 5 Epidermophyton floccosum positive patients, in 1 patient out of 2 Trichophyton violeoceum positive patients and none in the Trichophyton rubrum positive patients.

In one of the subject in the placebo arm of Tinea patients, the organism isolated at baseline was Trichophyton violaceum, while at the end of the study the organism isolated was Epidermophyton floccosum.

Table 17: Fungal Identification Results for Tinea patients

Treatment arm	Total no of patients(n)	Type	FC-V1	FC-V5	Species identified	
					Baseline	End of study
Test arm	9	Cruris	Positive	Negative	Epidermophyton floccosum	None
		Corporus	Positive	Negative	Trichophyton rubrum	None
		Pedis	Positive	Negative	Epidermophyton floccosum	None
		Cruris	Positive	Negative	Epidermophyton floccosum	None
		Cruris	Positive	Negative	Trichophyton violeoceum	None
		Corporus	Positive	Negative	Epidermophyton floccosum	None
		Cruris	Positive	Negative	Trichophyton rubrum	None
		Cruris	Positive	Negative	Epidermophyton floccosum	None
		Pedis	Positive	Negative	Epidermophyton floccosum	None
Placebo arm	9	Pedis	Positive	Negative	Epidermophyton floccosum	None
		Pedis	Positive	Positive	Epidermophyton floccosum	Epidermophyton floccosum
		Corporus	Positive	Positive	Epidermophyton floccosum	Epidermophyton floccosum
		Corporus	Positive	Positive	Trichophyton	Trichophyton

					rubrum	rubrum
		Corporus	Positive	Positive	Trichophyton rubrum	Trichophyton rubrum
		Pedis	Positive	Negative	Epidermophyton floccosum	None
		Pedis	Positive	Negative	Epidermophyton floccosum	None
		Corporus	Positive	Positive	Trichophyton violaceum	Epidermophyton floccosum
		Cruris	Positive	Negative	Trichophyton violeoceum	None
Test=Biovite® Dermaceutical formulation (lotion) Placebo=Placebo formulation (lotion) n=Number of patients with Tinea						

At baseline, in the test group of the Onychomycosis patients, fungal culture was positive in all 5 patients and organism isolated was Trichophyton rubrum in 2 patients, Trichophyton mentagrophytes in 2 patients and Epidermophyton floccosum in one patient. While at the end of the study, fungal culture was negative for all the patients.

At baseline, in the placebo group of the Onchomycosis patients, fungal culture was positive in all 5 patients and organism isolated was Epidermophyton floccosum in 2 patients, Trichophyton mentagrophytes in 2 patients and Trichophyton rubrum in one patient. While at the end of the study, fungal culture was negative for one patient out of one Trichophyton rubrum positive patient, in 1 patient out of 2 Trichophyton mentagrophytes positive patients and for none of the 2 Epidermophyton floccosum positive patients,.

Table 18: Fungal Identification Results for Onychomycosis patients

Treatment arm	Total no of patients(n)	FC-V1	FC-V5	Species Identified	
				Baseline	End of the study
Test arm	5	Positive	Negative	Trichophyton mentagrophytes	None
		Positive	Negative	Trichophyton rubrum	None
		Positive	Negative	Trichophyton rubrum	None
		Positive	Negative	Epidermophyton floccosum	None
		Positive	Negative	Trichophyton mentagrophytes	None
Placebo arm	5	Positive	Positive	Trichophyton mentagrophytes	Trichophyton mentagrophytes
		Positive	Positive	Epidermophyton floccosum	Epidermophyton floccosum
		Positive	Positive	Epidermophyton floccosum	Epidermophyton floccosum
		Positive	Negative	Trichophyton rubrum	None

		Positive	Negative	Trichophyton mentagrophytes	None

11.3.1.4 Size & severity score of target lesion of Tinea & Extent & severity score of target lesion of Onychomycosis

Size of the Tinea Lesion

Table 19 summarizes the size of target lesion of Tinea by visit and Table 20 summarizes the analysis of change from baseline at end of study in size of Tinea in target lesion in MITT population. At the screening visit, the size of the Tinea lesion ranged from 6 cms to 20 cms in the test group and 6 to 10cms in the placebo group. At the end of the study visit, the size of the Tinea lesion approximately varied from 1 cm to 4 cms in the test group while in the placebo group, the size of the lesion ranged from 5 cms to 15 cms.

The mean (SD) size of the Tinea lesion at baseline was about 13.3 (5.1) cms in the test group and at the end of the study visit it was reduced to 3.1cms (1.8). There was a reduction of around 10.2cms (3.7) from the baseline visit with respect to size of the Tinea. In the placebo group, the mean (SD) size of the Tinea lesion at baseline was about 8.0 (1.4) cms and at the end of the study visit it was about 8.8 (3.7) cms. There was an increase in the mean size of around 0.8cms (3.2) from the baseline visit with respect to size of the Tinea. The mean difference (Test-Placebo) was -11.0. The 95% C.I between the test and placebo group was (-14.47, -7.53) with a significant p-value of <0.0001.

Table 19: Summary of size of target lesion of Tinea by visit (Modified Intention to treat Population)

VISITS	Size of Tinea	Test (N=9)		Placebo (N=9)	
		n	%	n	%
VISIT 1	6	1	11.11	1	11.11
	7	0	0.00	3	33.33
	8	2	22.22	2	22.22
	9	0	0.00	1	11.11
	10	0	0.00	2	22.22
	12	1	11.11	0	0.00
	15	2	22.22	0	0.00
	18	2	22.22	0	0.00
	20	1	11.11	0	0.00
VISIT 2	5	2	22.22	1	11.11
	6	1	11.11	2	22.22
	7	0	0.00	3	33.33
	8	1	11.11	1	11.11
	9	0	0.00	2	22.22
	12	3	33.33	0	0.00
	14	1	11.11	0	0.00
	16	1	11.11	0	0.00

VISITS	Size of Tinea	Test (N=9)		Placebo (N=9)	
		n	%	n	%
VISIT 3	3	2	22.22	0	0.00
	4	1	11.11	0	0.00
	6	1	11.11	1	11.11
	7	1	11.11	4	44.44
	8	0	0.00	2	22.22
	9	1	11.11	1	11.11
	10	3	33.33	1	11.11
VISIT 4	2	3	33.33	0	0.00
	4	1	11.11	0	0.00
	5	1	11.11	0	0.00
	6	2	22.22	2	22.22
	7	1	11.11	3	33.33
	8	1	11.11	2	22.22
	9	0	0.00	1	11.11
	11	0	0.00	1	11.11
VISIT 5	1	2	22.22	0	0.00
	2	1	11.11	0	0.00
	3	3	33.33	0	0.00
	4	2	22.22	0	0.00
	5	0	0.00	2	22.22
	6	0	0.00	1	11.11
	7	1	11.11	1	11.11
	8	0	0.00	2	22.22
	12	0	0.00	1	11.11
	13	0	0.00	1	11.11
	15	0	0.00	1	11.11

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects reporting the extent score
Source Listing: Tinea assessment

Table 20: Analysis of change from baseline at End of study in Size of Tinea in target lesion (Modified Intention to treat Population)

Treatment .	N .	Mean (SD)			Between-group comparisons (Test-Placebo)		
		Baseline visit	End of study visit	Change§	Mean Difference †	95% C.I.	P-value*
Test	9	13.3 (5.1)	3.1 (1.8)	-10.2 (3.7)	-11.0	(-14.47, -7.53)	<.0001
Placebo	9	8.0 (1.4)	8.8 (3.7)	0.8 (3.2)			

Test=Biovite® Dermaceutical formulation (cream), Placebo=Placebo formulation (cream)
§ Change = size at visit 5 - size at baseline visit
† Difference = between-group difference in change from baseline visit
P-value*: P-value from two sample t test for change, 95% CI: 95% confidence interval from ttest procedure
Source listing: Tinea assessment

Severity score of Tinea lesion

Table 21 summarizes severity score of target lesion of Tinea by visit and Table 22 summarizes the analysis of change from baseline at End of study in severity score of Tinea in target lesion in MITT population. At the screening visit, the severity score of Tinea lesion ranged from a score of 8 to 10 both in the test group as well as in placebo group. While at the end of the study visit, most of the patients achieved decrease in severity score which ranged from 1 to 4 in the test group and 6 to 10 in the placebo group.

The mean (SD) severity score of Tinea lesion in the test group at baseline was about 9.0 (0.5) and at the end of the study visit, it reduced to 2.4 (0.9). There was a reduction in the severity score of about 6.6 (0.5) from the baseline visit. The mean (SD) severity score of Tinea lesion in the placebo group at baseline was about 8.9 (0.6) and at the end of the study visit, it was 8.1 (1.8). There was a reduction in the severity score only about 0.8 (2.0) from the baseline visit. The mean difference (Test-Placebo) was -5.78. The 95% C.I between the test and placebo group was (-7.32, -4.23) with a significant p-value of <0.0001.

Table 21: Summary of severity score of target lesion of Tinea by visit (Modified Intention to treat Population)

VISITS	Severity score	Test (N=9)		Placebo (N=9)	
		n	%	n	%
VISIT 1	8	1	11.11	2	22.22
	9	7	77.78	6	66.67
	10	1	11.11	1	11.11
VISIT 2	5	1	11.11	0	0.00
	6	3	33.33	0	0.00
	7	4	44.44	0	0.00
	8	1	11.11	5	55.56
	9	0	0.00	4	44.44
VISIT 3	4	1	11.11	0	0.00
	5	4	44.44	0	0.00
	6	4	44.44	0	0.00
	7	0	0.00	1	11.11
	8	0	0.00	4	44.44
	9	0	0.00	4	44.44
VISIT 4	2	1	11.11	0	0.00
	3	3	33.33	0	0.00

VISITS	Severity score	Test (N=9)		Placebo (N=9)	
		n	%	n	%
	4	3	33.33	0	0.00
	5	1	11.11	0	0.00
	6	1	11.11	1	11.11
	8	0	0.00	5	55.56
	9	0	0.00	3	33.33
VISIT 5	1	1	11.11	0	0.00
	2	4	44.44	0	0.00
	3	3	33.33	0	0.00
	4	1	11.11	0	0.00
	6	0	0.00	3	33.33
	8	0	0.00	2	22.22
	9	0	0.00	1	11.11
	10	0	0.00	3	33.33

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects reporting the severity score
Source Listing: Tinea assessment

Table 22: Analysis of change from baseline at End of study in severity score of Tinea in target lesion (Modified Intention to treat Population)

Treatment .	N .	Mean (SD)			Between-group comparisons (Test-Placebo)		
		Baseline visit	End of study visit	Change§	Mean Difference †	95% C.I.	P-value*
Test	9	9.0 (0.5)	2.4 (0.9)	-6.6 (0.5)	-5.78	(-7.32, -4.23)	<.0001
Placebo	9	8.9 (0.6)	8.1 (1.8)	-0.8 (2.0)			

Test=Biovite® Dermaceutical formulation (cream), Placebo=Placebo formulation (cream)
§ Change = size at visit 5 - size at baseline visit
† Difference = between-group difference in change from baseline visit
P-value*: P-value from two sample t test for change, 95% CI: 95% confidence interval from ttest procedure
Source listing: Tinea assessment

Surface area of Onychomycosis lesion

Table 23 represents the percentage of surface area of target area of Onychomycosis involved by visit and Table 24 represents the change from baseline at end of study in percentage of surface area involved in Onychomycosis in MITT population. the Affected surface area in case of Onychomycosis varied from 60-70% in both test and placebo group at the screening visit. However at the end of the study visit, the affected surface area got reduced to 10-25% in the test group and 45-55% in the placebo group.

The mean (SD) percentage of affected surface area for Onychomycosis lesion in the test group at baseline was about 63.0% (4.5) and at the end of the study, it decreased to 18.0% (5.7). There was a reduction in the mean percentage of surface area of about 45% (5.0) from baseline visit. The mean (SD) percentage of affected surface area in the placebo group at baseline was about 66.0% (5.5) and at the end of the visit it was about 51.0% (4.2). There was a reduction in the mean percentage of surface area of about 15% (7.9) from the baseline visit. The mean difference (Test-Placebo) was -30.0. The 95% C.I between the test and placebo group was (-39.65, -20.35) with a significant p-value of <0.0001.

Table 23: Percentage of surface area of target area of Onychomycosis involved by visit (Modified Intention to treat Population)

VISITS	%Surface area	Test (N=5)		Placebo (N=5)	
		n	%	n	%
VISIT 1	60	3	60.00	2	40.00
	65	1	20.00	0	0.00
	70	1	20.00	3	60.00
VISIT 2	50	3	60.00	1	20.00
	55	1	20.00	1	20.00
	60	1	20.00	3	60.00
VISIT 3	30	1	20.00	0	0.00
	40	3	60.00	0	0.00
	50	0	0.00	2	40.00
	55	0	0.00	2	40.00
	60	1	20.00	1	20.00
VISIT 4	20	1	20.00	0	0.00
	25	1	20.00	0	0.00
	30	2	40.00	0	0.00
	40	1	20.00	0	0.00
	50	0	0.00	4	80.00
	55	0	0.00	1	20.00
VISIT 5	20	2	40.00	0	0.00
	25	1	20.00	0	0.00
	30	2	40.00	0	0.00
	50	0	0.00	4	80.00
	55	0	0.00	1	20.00
VISIT 6	15	2	40.00	0	0.00
	20	1	20.00	0	0.00
	25	2	40.00	0	0.00
	50	0	0.00	2	40.00
	55	0	0.00	3	60.00

VISITS	%Surface area	Test (N=5)		Placebo (N=5)	
		n	%	n	%
VISIT 7	10	1	20.00	0	0.00
	15	1	20.00	0	0.00
	20	2	40.00	0	0.00
	25	1	20.00	0	0.00
	45	0	0.00	1	20.00
	50	0	0.00	2	40.00
	55	0	0.00	2	40.00

Test=Biovite® Dermaceutical formulation (lotion)
Placebo=Placebo formulation (lotion)
n/%=Number / percentage of subjects reporting the %Surface area
Source Listing: Onychomycosis assessment

Table 24: Analysis of change from baseline at End of study in Percentage of surface area involved in Onychomycosis (Modified Intention to treat Population)

Treatment.	N.	Mean (SD)			Between-group comparisons (Test-Placebo)		
		Baseline visit	End of study visit	Change§	Mean Difference †	95% C.I.	P-value*
Test	5	63.0 (4.5)	18.0 (5.7)	-45.0 (5.0)	-30.0	(-39.65, -20.35)	<.0001
Placebo	5	66.0 (5.5)	51.0 (4.2)	-15.0 (7.9)			

Test=Biovite® Dermaceutical formulation (lotion), Placebo=Placebo formulation (lotion)
§ Change = size at visit 5 - size at baseline visit
† Difference = between-group difference in change from baseline visit
P-value*: P-value from two sample t test for change, 95% CI: 95% confidence interval from ttest procedure
Source listing: Onychomycosis assessment

Extent and severity score of Onychomycosis lesion

Table 25 summarizes the extent and severity score of target lesion and Table 26 summarizes the analysis of change from baseline at end of study in extent and severity score of target lesion of Onychomycosis in MITT population. At the screening visit the extent and severity score of Onychomycosis lesion was about 3 for both test and the placebo group. While at the end of the study visit the score decreased to 1 in the test group and 2 to 3 in placebo group.

The mean (SD) of extent and severity score of Onychomycosis lesion in the test group at baseline was about 3.00 (0.0) and at the end of the study visit it decreased to 1.00 (0.0). The reduction in the severity score was about 2.0 (0.0) from the baseline visit. At baseline visit, the mean (SD) of extent and the severity score in the placebo group was about 3.00 (0.0) and at the end of the study visit it was about 2.8 (0.4). The reduction in the severity score was only about 0.2 (0.4) from the baseline visit. The mean difference (Test-Placebo) was -1.8. The 95% C.I between the test and placebo group was (-2.36, -1.24)

with a significant p-value of 0.0008.

Table 25: Summary of extent and severity score of target lesion of Onychomycosis by visit (Modified Intention to treat Population)

VISITS	Extent and severity score	Test (N=5)		Placebo (N=5)	
		n	%	n	%
VISIT 1	3	5	100.00	5	100.00
VISIT 2	2	4	80.00	1	20.00
	3	1	20.00	4	80.00
VISIT 3	2	5	100.00	1	20.00
	3	0	0.00	4	80.00
VISIT 4	1	5	100.00	0	0.00
	2	0	0.00	1	20.00
	3	0	0.00	4	80.00
VISIT 5	1	4	80.00	0	0.00
	2	0	0.00	1	20.00
	3	1	20.00	4	80.00
VISIT 6	1	5	100.00	0	0.00
	2	0	0.00	1	20.00
	3	0	0.00	4	80.00
VISIT 7	1	5	100.00	0	0.00
	2	0	0.00	1	20.00
	3	0	0.00	4	80.00

Test=Biovite® Dermaceutical formulation (lotion)
Placebo=Placebo formulation (lotion)
n/%=Number / percentage of subjects reporting the extent and severity score
Source Listing: Onychomycosis assessment

Table 26: Analysis of change from baseline at End of study in extent and severity score of target lesion of Onychomycosis (Modified Intention to treat Population)

Treatment .	N .	Mean (SD)			Between-group comparisons (Test-Placebo)		
		Baseline visit	End of study visit	Change§	Mean Difference †	95% C.I.	P-value*
Test	5	3.0 (0.0)	1.0 (0.0)	-2.0 (0.0)	-1.8	(-2.36, -1.24)	.0008
Placebo	5	3.0 (0.0)	2.8 (0.4)	-0.2 (0.4)			

Test=Biovite® Dermaceutical formulation (lotion), Placebo=Placebo formulation (lotion)
§ Change = size at visit 5 - size at baseline visit
† Difference = between-group difference in change from baseline visit
P-value*: P-value from two sample t test for change, 95% CI: 95% confidence interval from ttest procedure
Source listing: Onychomycosis assessment

11.3.1.5 IGA score

Table 27,

Table 28 and Table 29 summarizes the investigator global assessment response of cleared or excellent by visit for patients with Tinea and/or Onychomycosis in MITT population respectively.

At the end of study in the test group of Tinea patients, IGA response of "cleared" was achieved in 3 (33.33%) patients and the IGA response of "excellent" was achieved in 6 (66.67%) patients. While in the placebo group, IGA response of "cleared" and IGA response of "excellent" was not achieved in any of the patients.

At visit 4, in the test group of Onychomycosis patients, IGA response of "cleared" was achieved in 3 (60%) patients and IGA response of "excellent" was achieved in 2 (40%) of patients. At visit 7, IGA response of "excellent" was achieved in all the 5 (100%) patients. However in the placebo group, at visit 4 as well as at the end of the study visit, IGA response of "cleared" and IGA response of "excellent" was not achieved in any of patients.

For tinea subjects, 9 out of 9 test subjects (100.00%) achieved clinical/mycological cure (defined as an IGA response of "cleared" or "excellent") from visit 2 until the end of the study compared to none of the placebo subjects. For Onychomycosis subjects, 5 of 5 test subjects (100%) achieved clinical/mycological cure from visit 3 until the end of the study compared to none of the placebo subjects.

Table 27: Summary of investigator global assessment response of cleared or excellent by visit for patients with Tinea (Modified Intention to treat Population)

VISITS	Test (N=9)				Placebo (N=9)			
	Cleared		Excellent		Cleared		Excellent	
	n	%	n	%	n	%	n	%
VISIT 2	1	11.11	0	0.00	0	0.00	0	0.00
VISIT 3	9	100.00	0	0.00	0	0.00	0	0.00
VISIT 4	7	77.78	2	22.22	0	0.00	0	0.00
VISIT 5	3	33.33	6	66.67	0	0.00	0	0.00

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects in 'Cleared' or 'Excellent' category as assessed by the investigator
Source Listing: Physician assessment of treatment response

Table 28: Summary of investigator global assessment response of cleared or excellent by visit for patients with Onychomycosis (Modified Intention to treat Population)

VISITS	Test (N=5)				Placebo (N=5)			
	Cleared		Excellent		Cleared		Excellent	
	n	%	n	%	n	%	n	%
VISIT 3	2	40.00	0	0.00	0	0.00	0	0.00
VISIT 4	3	60.00	2	40.00	0	0.00	0	0.00
VISIT 5	3	60.00	2	40.00	0	0.00	0	0.00
VISIT 6	0	0.00	5	100.00	0	0.00	0	0.00
VISIT 7	0	0.00	5	100.00	0	0.00	0	0.00

Test=Biovite® Dermaceutical formulation (lotion)
Placebo=Placebo formulation (lotion)
n/%=Number / percentage of subjects in 'Cleared' or 'Excellent' category as assessed by the investigator
Source Listing: Physician assessment of treatment response

Table 29: Summary of investigator global assessment response of cleared or excellent by visit for subjects with Tinea and Onychomycosis (Modified Intention to treat Population)

VISITS	Test (N=14)				Placebo (N=14)			
	Cleared		Excellent		Cleared		Excellent	
	n	%	n	%	n	%	n	%
VISIT 2	1	7.14	0	0.00	0	0.00	0	0.00
VISIT 3	11	78.57	0	0.00	0	0.00	0	0.00
VISIT 4	10	71.43	4	28.57	0	0.00	0	0.00
VISIT 5	6	42.86	8	57.14	0	0.00	0	0.00
VISIT 6	0	0.00	5	35.71	0	0.00	0	0.00
VISIT 7	0	0.00	5	35.71	0	0.00	0	0.00

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects in 'Cleared' or 'Excellent' category as assessed by the investigator
Source Listing: Physician assessment of treatment response

11.3.1.6 Assessment of the lesions by photographs

Table 30, Table 31 and Table 32 summarizes improvement in lesions assessed by photographic record at baseline and at end of study for Tinea and/or Onchyomycosis patients in MITT population. Photographic record at the end of the study visit showed improvement in Tinea lesions in all the 9 (100%) test group patients, while in placebo group none of the patients showed any improvement. In Onychomycosis patients,

photographic record at the end of the study showed improvement in all the 5 (100%) test group patients, while in the placebo group none of the patients showed any improvement.

Table 30: Summary Improvement in lesions assessed by photographic record at baseline and at end of study for Tinea (Modified Intention to treat Population)

Test (N=9)				Placebo (N=9)			
No		Yes		No		Yes	
n	%	n	%	n	%	n	%
0	0.00	9	100.00	9	100.00	0	0.00

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects in 'Yes' or 'No' category as assessed by the investigator for photographic record
Source Listing: Physician assessment of treatment response

Table 31: Summary Improvement in lesions assessed by photographic record at baseline and at end of study for Onychomycosis (Modified Intention to treat Population)

Test (N=5)				**Placebo (N=5)**			
No		**Yes**		**No**		**Yes**	
n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
0	0.00	5	100.00	5	100.00	0	0.00

Test=Biovite® Dermaceutical formulation (lotion)
Placebo=Placebo formulation (lotion)
n/%=Number / percentage of patients in 'Yes' or 'No' category as assessed by the investigator for photographic record
Source Listing: Physician assessment of treatment response

Table 32: Summary Improvement in lesions assessed by photographic record at baseline and at end of study Tinea and Onychomycosis (Modified Intention to treat Population)

Test (N=14)				Placebo (N=14)			
No		Yes		No		Yes	
n	%	n	%	n	%	n	%
0	0.00	14	100.00	14	100.00	0	0.00

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects in 'Yes' or 'No' category as assessed by the investigator for photographic record
Source Listing: Physician assessment of treatment response

11.3.2 Statistical Issues

There were no statistical issues. Statistical analyses used and handling of dropouts and missing data are summarized in section 9.7.1 and 9.7.2 of this clinical study report, respectively, and a detailed documentation of statistical methods is presented in Appendix 16.1.9.

11.3.2.1 Adjustment for Covariates

Descriptive statistics was used to analyze the secondary efficacy endpoint with factors for baseline, treatment and center with baseline lesion count as a covariate.

11.3.2.2 Handling of dropouts or missing data

All missing data was imputed using the last observation carried forward after baseline for the modified intention-to-treat and no imputation was done for the per protocol analysis.

11.3.2.3 Interim Analyses

No interim analysis was planned for the study.

11.3.3 Tabulation of Individual Response Data

A line listing of efficacy data is provided in Appendix 16.2.6.

11.3.4 Drug Dose, Drug Concentration, and Relationships to Response

Not Applicable

11.3.5 Drug-Drug and Drug-Disease Interactions

Not Applicable

11.3.6 By-Patient Displays

Not provided.

11.3.7 Efficacy Conclusions

At the end of the study, in the test group, KOH smear was negative in 13 (92.86%) patients, fungal culture was negative in all 14 (100.00%) patients and all 14 (100.00%) patients showed no spore count. While in placebo group, at the end of the study KOH smear was positive in all 14 (100.00%) of patients, fungal culture was positive in 8 (57.14%) patients and 8 (57.14%) patients showed positivity for live spore count.

At the end of the study, the mycological cure was achieved in 13 (92.9%) out of 14 patients assessed by KOH smear and in all 14 (100%) patients assessed by fungal culture and by spore counts in the test group. Mycological cure showed significance when the test group was compared with the placebo group with p-values of <0.001, 0.0019 and 0.0019 with respect to KOH smear, fungal culture and live spore count respectively.

Tinea

At the end of the study, the mean (SD) size and severity score of tinea lesion was 3.1 (1.8) cms and 2.4 (0.9) in the test group and 8.8 (3.7) cms and 8.1 (1.8) in the placebo group respectively. The reduction in the mean size and severity score from the baseline visit was about 10.2cms (3.7) and 6.6 (0.5) in the test group and 0.8cms (3.2) and 0.8 (2.0) in the placebo group respectively. Size and severity score of Tinea lesion showed significance when the test group was compared to placebo group with a p-value of <0.0001.

IGA response of "cleared" was achieved in 3 (33.33%) and the IGA response of "excellent" was achieved in 6 (66.67%) patients. While in the placebo group, IGA response of "cleared" and IGA response of "excellent" was not achieved in any of the patients. Photographic record at the end of the study visit showed improvement in Tinea lesions in all the 9 (100%) test group patients, while in placebo group none of the patients showed any improvement.

At the end of the study in the test arm, fungal culture was negative for all the organisms identified at the baseline (Epidermophyton floccosum in 6 patients, Trichophyton rubrum in 2 patients and Trichophyton violeoceum in one patient). While at the end of the study, fungal culture was negative for 3 patients out of 5 Epidermophyton floccosum positive patients, in 1 patient out of 2 Trichophyton violeoceum positive patients and none in the Trichophyton rubrum positive patients. In one of the subject in the placebo arm of Tinea patients, the organism isolated at baseline was Trichophyton violaceum, while at the end of the study the organism isolated was Epidermophyton floccosum possibly indicating reinfection.

Onychomycosis

At the end of the study, the mean (SD) percentage of surface area and extent and severity score of Onychomycosis lesion was 18.0% (5.7) and 1.00 (0.0) in the test group and 51.0% (4.2) and 2.8 (0.4) in the placebo group respectively. The reduction in the mean percentage of surface area and severity score from the baseline visit was 45% (5.0) and 2.0 (0.0) in the test group and 15% (7.9) and 0.2 (0.4) in the placebo group respectively. Surface area and severity score of Onychomycosis lesion showed significance when the test group was compared to placebo group with a p-value of <0.0001 and 0.0008 respectively.

IGA response of "excellent" was achieved in all the 5 (100%) patients and in the placebo group IGA response of "cleared" and IGA response of "excellent" was not achieved in any of patients. Photographic record at the end of the study showed improvement in all the 5 (100%) test group patients, while in the placebo group none of the patients showed any improvement.

At the end of the study in the test arm, fungal culture was negative for 3 patients out of 3 Trichophyton rubrum positive patients and in 2 patients out of 2 Trichophyton

mentagrophytes positive patients. While in the placebo arm, fungal culture was negative for none of the 2 Epidermophyton floccosum positive patients, for one patient out of one Trichophyton rubrum positive patient and in 1 patient out of 2 Trichophyton mentagrophytes positive patients.

12 SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

A total of 28 patients were randomized to receive Biovite®'s Calmagen™ Dermaceutical cream or lotion & placebo cream & lotion for a period of 2 to 12 weeks.

12.2 ADVERSE EVENTS (AE'S)

12.2.1 Brief Summary of Adverse Events

The proportion of patients with AEs was summarized by the treatment that the patient received at the time of occurrence of AE during the study period. The severity of AEs was graded as mild, moderate or severe and the relationship as definite, probably, possibly, unlikely and unrelated to the treatment by the investigator.

Out of 28 patients, those receiving Biovite®'s Calmagen™ Dermaceutical cream or lotion did not experience any adverse event, while one patient on placebo cream or lotion experienced leg pain in both legs, which was mild & not related to the study medication.

12.2.2 Display of Adverse Events

Adverse events are shown in Table 33, Table 34 and Table 35.

Table 33: Number (and percentage) of patients with treatment-emergent adverse events classified by AE term during the study (Safety Population)

AE term	Test (N=14)		Placebo (N=14)	
	n	%	n	%
At Least One Symptom	0	0.0	1	7.1
Leg Pain Both Legs	0	0.0	1	7.1

Test=Biovite® Dermaceutical formulation (cream or lotion)
Placebo=Placebo formulation (cream or lotion)
At least one symptom=At least one symptom experienced regardless of the AE term
n/%=Number/percentage of patients reporting at least once a specified symptom during the treatment
Source Listing: Adverse Event

Table 34: Number (and percentage) of patients with mild, moderate, severe and very severe treatment-emergent adverse events classified by AE term during the study (Safety Population)

AE term	Mild				Moderate				Severe				very severe			
	Test (N=14)		Placebo (N=14)		Test (N=14)		Placebo (N=14)		Test (N=14)		Placebo (N=14)		Test (N=14)		Placebo (N=14)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
At Least One Symptom	0	0.00	1	7.14	0	0.00	0	0.00	0	0.00	0	0.00	0	0	0	0.00
Leg Pain Both Legs	0	0.00	1	7.14	0	0.00	0	0.00	0	0.00	0	0.00	0	0	0	0.00

Test=Biovite® Dermaceutical formulation (cream or lotion)
Placebo=Placebo formulation (cream or lotion)
At least one symptom=At least one symptom experienced regardless of the AE term
n/%=Number/percentage of patients reporting at least once a specified symptom during the treatment
Source Listing: Adverse Event

Table 35: Number (and percentage) of patients with treatment-emergent AE term during the study assessed as Unrelated, Remote/Unlikely, Possible, Probable and Definite (Safety Population)

AE term	Unrelated				Remote/Unlikely				Possible				Probable				Definite			
	Test (N=14)		Placebo (N=14)		Test (N=14)		Placebo (N=14)		Test (N=14)		Placebo (N=14)		Test (N=14)		Placebo (N=14)		Test (N=14)		Placebo (N=14)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
At Least One Symptom	0	0.00	1	7.14	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Leg Pain Both Legs	0	0.00	1	7.14	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Test=Biovite® Dermaceutical formulation (cream or lotion)
Placebo=Placebo formulation (cream or lotion)
At least one symptom=At least one symptom experienced regardless of the AE term
n/%=Number/percentage of patients reporting at least once a specified symptom during the treatment
Source Listing: Adverse Event

12.2.3 Analysis of Adverse Events

Patients in the Biovite®'s Calmagen™ Dermaceutical cream or lotion group did not report any adverse event but one patient in placebo group reported leg pain in both legs which was mild & not related to the study medication.

There were no AEs reported in either of the group related to the study medication.

12.2.4 Listing of Adverse Events by Patient

Refer appendix 16.2.7

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT AE

No deaths, other SAEs and other significant AE(s) were reported in this study.

12.3.1 Listings of Deaths, other SAEs and other Significant AEs

Not Applicable

12.3.2 Narratives of Deaths, Other SAEs and Other significant AEs

Not Applicable

12.3.3 Analysis and Discussions of Deaths, Other SAEs and Other Significant AEs

Not Applicable

12.4 CLINICAL LABORATORY EVALUATION

12.4.1 Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

Not applicable

12.4.2 Evaluation of Each Laboratory Parameter

Not applicable

12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

12.5.1 Vital Signs

Vital signs were found to be within the normal range for all patients during the course of the study. There were no clinically significant abnormal findings at any of the visits in both test group & placebo group. **Error! Reference source not found.** provides the summary of vital signs by treatment.

12.5.2 Physical Findings

Physical examination was found to be normal during the course of the study for all the patients. There were no clinically significant abnormal findings at any of the visits.

12.6 CONCOMITANT MEDICATIONS

Table 36 provides the number and percentage of patients who used concomitant medications during the study period by treatment group, for the safety population.

Table 36: Number (and percentage) of patients who used concomitant medication during study (Safety Population)

Medical Term	Test (N=14)		Placebo(N=14)	
	n	%	n	%
Any medication	0	0.0	1	7.1
Paracetamol+500mg	0	0.0	1	7.1

Test=Biovite® Dermaceutical formulation (cream or lotion)
Placebo=Placebo formulation (cream or lotion)
n/%= Number/Percentage of patients who started taking any concomitant medication at least once during the study
Source Listing: Concomitant medication

12.7 SAFETY CONCLUSIONS

There were no AEs reported in the test group while in the placebo group, a patient reported pain in both the legs, which was mild & not related to the study medication. The concomitant medication used was considered safe during the study period.

There were no adverse events reported which was related to the study drug. There were no serious adverse events reported in the study. The study medication was found to be safe having comparable safety profile to that of placebo.

13 DISCUSSIONS AND OVERALL CONCLUSIONS

This was a double blinded, placebo controlled, parallel-group, randomized, comparative study to assess the fungicidal profile, efficacy and safety of the Biovite®'s Calmagen™ Dermaceutical cream & lotion. This study was aimed to demonstrate the superior efficacy of Biovite®'s Calmagen™ Dermaceutical cream & lotion with placebo in the topical treatment of Tinea. To achieve this objective a primary end point of mycological cure was chosen as appropriate. Mycological cure, in the sense meant negative KOH smear, fungal culture and live spore count.

At the end of the study, in the test group, KOH smear was negative in 13 (92.86%) patients, fungal culture was negative in all 14 (100.00%) patients and all 14 (100.00%) patients showed no spore count. While in placebo group, at the end of the study KOH

smear was positive in all 14 (100.00%) of patients, fungal culture was positive in 8 (57.14%) patients and 8 (57.14%) of patients showed positivity for live spore count.

At the end of the study, the mycological cure was achieved in 13 (92.9%) out of 14 patients assessed by KOH smear and in all 14 (100%) patients assessed by fungal culture and by spore counts in the test group. Mycological cure showed significance when the test group was compared with the placebo group with p-values of <0.001, 0.0019 and 0.0019 with respect to KOH smear, fungal culture and live spore count respectively

For Tinea, fungal culture was negative for all the organisms identified at the baseline (Epidermophyton floccosum, Trichophyton rubrum and Trichophyton violeoceum) in the test group. While in placebo group, at the end of the study KOH smear was positive in all 14 (100.00%) of patients, fungal culture was positive in 8 (57.14%) patients and 8 (57.14%) of patients showed positivity for live spore count and fungal culture was negative for 3 patients out of 5 Epidermophyton floccosum positive patients, in 1 patient out of 2 Trichophyton violeoceum positive patients and none in the Trichophyton rubrum positive patients and in one of the subject, the organism isolated at baseline was Trichophyton violaceum, while at the end of the study the organism isolated was Epidermophyton floccosum possibly indicating reinfection. Thus, test group showed superior results in terms of efficacy for Tinea compared to placebo.

For Onychomycosis, fungal culture was negative for 3 patients out of 3 Trichophyton rubrum positive patients and in 2 patients out of 2 Trichophyton mentagrophytes positive patients in the test group. While in placebo group, KOH smear was positive in 80% of patients, fungal culture was positive in 60% of patients, 60% of patients showed live spore counts and fungal culture was negative for 1 patient out of 3 Epidermophyton floccosum positive patients and in 1 patient out of 2 Trichophyton mentagrophytes positive patients. Here as well, test group showed superior efficacy results compared to placebo.

The study met the primary end point for proving superiority of Biovite®'s Calmagen™ Dermaceutical cream & lotion over placebo. Hence it can be concluded that the Biovite®'s Calmagen™ Dermaceutical cream & lotion is superior in efficacy compared to placebo in the topical treatment of Tinea.

The secondary endpoints considered for this study were size and severity score of Tinea, surface area and extent/severity score of Onychomycosis, IGA sore and photographic assessment.

For Tinea, at the end of the study, the mean (SD) size and severity score of tinea lesion was 3.1 (1.8) cms and 2.4 (0.9) in the test group and 8.8cms (3.7) and 8.1 (1.8) in the placebo group respectively. The reduction in the mean size and severity score from the baseline visit was about 10.2cms (3.7) and 6.6 (0.5) in the test group and 0.8cms (3.2) and 0.8 (2.0) in the placebo group respectively. Size and severity score of Tinea lesion showed significance when the test group was compared to placebo group with a p-value

of <0.0001. IGA response of "cleared" was achieved in 3 (33.33%) and the IGA response of "excellent" was achieved in 6 (66.67%) patients and none in the placebo group patients. Photographic record showed 9 (100%) improvement in test group however in the placebo group none of the patients showed any improvement.

For Onychomycosis, at the end of the study, the mean (SD) percentage of surface area and extent and severity score of Onychomycosis lesion was 18.0% (5.7) and 1.00 (0.0) in the test group and 51.0% (4.2) and 2.8 (0.4) in the placebo group respectively. The reduction in the mean percentage of surface area and severity score from the baseline visit was 45% (5.0) and 2.0 (0.0) in the test group and 15% (7.9) and 0.2 (0.4) in the placebo group respectively. Surface area and severity score of Onychomycosis lesion showed significance when the test group was compared to placebo group with a p-value of <0.0001 and 0.0008 respectively.

IGA response of "excellent" was achieved in all the 5 (100%) patients and in the placebo group IGA response of "cleared" and IGA response of "excellent" was not achieved in any of patients. Photographic record showed improvement in all the 5 (100%) test group patients and placebo group patients showed no improvement.

No SAEs were reported in this study. Only one AE was reported in this study that belonged to placebo group. The study medication was found to be safe having comparable safety profile to that of placebo.

Thus, we can conclude that Biovite®'s Calmagen™ Dermaceutical cream & lotion showed superior efficacy and similar safety profile as that of placebo.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN TEXT

14.1 DEMOGRAPHIC DATA

Post Text Table 1: Number of subjects included and excluded from Safety MITT and PP analyses with reasons for exclusion of Tinea patients

Patient Status	Test (N=9)		Placebo (N=9)		ALL (N=18)	
	A	%	B	%	n	%
Number of patients enrolled	9	100.0	9	100.0	18	100.0
Included in the Modified-Intention-to-treat analysis	9	100.0	9	100.0	18	100.0
Included in the Per-Protocol analysis	9	100.0	9	100.0	18	100.0
Included in the Safety analysis	9	100.0	9	100.0	18	100.0
Test= Biovite Dermaceutical formulation (cream) Placebo= Placebo formulation (cream) Source Listing: Randomization, Inclusion/Exclusion, End of study						

Post Text Table 2: Number of subjects included and excluded from Safety MITT and PP analyses with reasons for exclusion of Onychomycosis patients

Patient Status	Test (N=5)		Placebo (N=5)		ALL (N=10)	
	n	%	n	%	n	%
Number of patients enrolled	5	100.0	5	100.0	10	100.0
Included in the Modified-Intention-to-treat analysis	5	100.0	5	100.0	10	100.0
Included in the Per-Protocol analysis	5	100.0	5	100.0	10	100.0
Included in the Safety analysis	5	100.0	5	100.0	10	100.0
Test= Biovite Dermaceutical formulation (lotion) Placebo= Placebo formulation (lotion) Source Listing: Randomization, Inclusion/Exclusion, End of study						

Post Text Table 3: Number of patients with Tinea at each visit (Modified-Intention-to-treat Population)

Visit	Test (N=9)	Placebo (N=9)	All (N=18)
SCREENING & RANDOMIZATION (VISIT1-V1)	9	9	18
VISIT 2	9	9	18
VISIT 3	9	9	18
VISIT 4	9	9	18
VISIT 5	9	9	18
Test= Biovite® Dermaceutical formulation (Cream) Placebo= Placebo formulation (Cream) Source listing: Date of Visit.			

Post Text Table 4: Number of patients with Onychomycosis at each visit (Modified-Intention-to-treat Population)

Visit	Test (N=9)	Placebo (N=9)	All (N=10)
SCREENING & RANDOMIZATION (VISIT1-V1)	5	5	10
VISIT 2	5	5	10
VISIT 3	5	5	10
VISIT 4	5	5	10
VISIT 5	5	5	10
VISIT 6	5	5	10
VISIT 7	5	5	10
Test= Biovite® Dermaceutical formulation (lotion) Placebo= Placebo formulation (lotion) Source listing: Date of Visit.			

Post Text Table 5: Summary of patient demographic characteristics at screening: categorical variables of Tinea (Modified-Intention-to-treat Population)

Variable	Categories	Test (N=9)		Placebo (N=9)		ALL (N=18)	
		n	%	n	%	n	%
Gender	Female	4	44.4	2	22.2	6	33.3
	Male	5	55.6	7	77.8	12	66.7
Race	Asian	9	100.0	9	100.0	18	100.0
Test= Biovite® Dermaceutical formulation (Cream) Placebo= Placebo formulation (Cream) n/%= Number/Percentage of patients with the given characteristics Source listing: Demography.							

Post Text Table 6: Summary of patient demographic characteristics at screening: continuous variables of Tinea (Modified-Intention-to-treat Population)

Variable	Categories	Test	Placebo	ALL
Age(in years)	N	9	9	18
	Mean	39.0	46.3	42.7
	SD	7.90	11.63	10.34
	Median	40.4	47.8	40.7
	Min	23.1	32.5	23.1
	Max	48.1	67.1	67.1
Height(cm)	N	9	9	18
	Mean	163.3	168.2	165.8
	SD	7.81	5.97	7.20
	Median	166.0	170.0	167.5
	Min	152.0	157.0	152.0
	Max	174.0	174.0	174.0
Weight(kg)	N	9	9	18

Variable	Categories	Test	Placebo	ALL
	Mean	64.3	69.2	66.8
	SD	9.19	8.96	9.16
	Median	62.0	70.0	68.5
	Min	53.0	53.0	53.0
	Max	76.0	82.0	82.0

N = Number of subjects with non-missing values
Test= Biovite® Dermaceutical formulation (Cream)
Placebo= Placebo formulation (Cream)
Source listing: Demography.

Post Text Table 7: Summary of patient demographic characteristics at screening: categorical variables of Onychomycosis (Modified-Intention-to-treat Population)

Variable	Categories	Test (N=5)		Placebo (N=5)		ALL (N=10)	
		n	%	n	%	n	%
Gender	Female	1	20.0	1	20.0	2	20.0
	Male	4	80.0	4	80.0	8	80.0
Race	Asian	5	100.0	5	100.0	10	100.0

Test= Biovite® Dermaceutical formulation (lotion)
Placebo= Placebo formulation (lotion)
n/%= Number/Percentage of patients with the given characteristics
Source listing: Demography.

Post Text Table 8: Summary of patient demographic characteristics at screening: continuous variables of Onychomycosis (Modified-Intention-to-treat Population)

Variable	Categories	Test	Placebo	ALL
Age(in years)	N	5	5	10
	Mean	33.8	44.9	39.3
	SD	11.82	14.71	13.87
	Median	27.7	48.1	42.5
	Min	22.7	20.0	20.0
	Max	51.6	57.7	57.7
Height(cm)	N	5	5	10
	Mean	168.6	168.8	168.7
	SD	4.22	4.97	4.35
	Median	170.0	169.0	169.5
	Min	162.0	161.0	161.0
	Max	172.0	174.0	174.0
Weight(kg)	N	5	5	10
	Mean	61.4	65.8	63.6
	SD	7.99	10.59	9.14
	Median	60.0	70.0	65.0
	Min	50.0	49.0	49.0

Variable	Categories	Test	Placebo	ALL
	Max	70.0	74.0	74.0

N = Number of patients with non-missing values
Test= Biovite® Dermaceutical formulation (lotion)
Placebo= Placebo formulation (lotion)
Source listing: Demography.

Post Text Table 9: Summary of number of subjects by Tinea involving area (type) at baseline (Modified-Intention-to-treat Population)

Tinea affected area	Test (N=9)		Placebo (N=9)	
	n	%	n	%
Extremities	0	0.0	1	11.1
Face	0	0.0	1	11.1
Groin	5	55.6	1	11.1
Others	2	22.2	1	11.1
Trunk	0	0.0	1	11.1
Webspaces	2	22.2	4	44.4

Test= Biovite® Dermaceutical formulation (cream)
Placebo= Placebo formulation (cream)
n/%= Number/Percentage of subjects reporting the specified Tinea involving area
Source listing: Tinea assessment

14.2 EFFICACY DATA (PER PROTOCOL)

Post Text Table 10: Summary of KOH smear by visit for patients with Tinea (Modified Intention to treat Population)

VISIT	Test (N=9)				Placebo (N=9)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	9	100.00	0	0.00	9	100.00	0	0.00
End of study	1	11.11	8	88.89	9	100.00	0	0.00

End of study = visit 5
Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of patients with the Tinea scrapings test done
Source Listing: Tinea scrapings

Post Text Table 11: Summary of KOH smear by visit for patients with Onychomycosis (Modified Intention to treat Population)

VISIT	Test (N=5)				Placebo (N=5)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	5	100.00	0	0.00	5	100.00	0	0.00
End of study	0	0.00	5	100.00	5	100.00	0	0.00

End of study = visit 7
Test=Biovite® Dermaceutical formulation (lotion)
Placebo=Placebo formulation (lotion)
n/% = Number/percentage of patients with the Onychomycosis scrapings test done
Source Listing: Onychomycosis scrapings

Post Text Table 12: Summary of KOH smear by visit for patients with Tinea (Per-protocol Population)

VISIT	Test (N=9)				Placebo (N=9)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	9	100.00	0	0.00	9	100.00	0	0.00
End of study*	1	11.11	8	88.89	9	100.00	0	0.00

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects with Tinea
Source Listing: Tinea scrapings

Post Text Table 13: Summary of KOH smears by visit for patients with Onychomycosis (Per-protocol Population)

VISIT	Test (N=5)				Placebo (N=5)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	5	100.00	0	0.00	5	100.00	0	0.00
End of study*	0	0.00	5	100.00	5	100.00	0	0.00

Test=Biovite® Dermaceutical formulation (lotion)
Placebo=Placebo formulation (lotion)
n/%=Number / percentage of subjects with Onychomycosis
Source Listing: Onychomycosis scrapings

Post Text Table 14: Summary of KOH smear by visit for patients with Tinea and Onychomycosis (Per-protocol Population)

VISIT	Test (N=14)				Placebo (N=14)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	14	100.00	0	0.00	14	100.00	0	0.00
End of study*	1	7.14	13	92.86	14	100.00	0	0.00

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects with Tinea
Source Listing: Tinea scrapings

Post Text Table 15: Analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by KOH smear for subjects with Tinea (Modified Intention to treat Population)

Treatment	KOH smear			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	9	0 (0 %)	0 (0 %)	0 (0 %)	(0.0 ,0.0)	0.0004
Test	9	0 (0 %)	8 (88.9 %)	8 (88.9 %)	(68.4 ,100.0)	

- End of study for the patients with Tinea is considered as visit 5
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n = Number of subjects with the Tinea scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 16: Analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by KOH smear for subjects with Tinea (Per-Protocol Population)

Treatment	KOH smear			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	9	0 (0 %)	0 (0 %)	0 (0 %)	(0.0 ,0.0)	0.0004
Test	9	0 (0 %)	8 (88.9 %)	8 (88.9 %)	(68.4 ,100.0)	

- End of study for the patients with Tinea is considered as visit 5
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n = Number of subjects with the Tinea scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 17: Analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by KOH smear for subjects with Onychomycosis (Modified Intention to treat Population)

Treatment	KOH smear			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	5	0 (0 %)	0 (0 %)	0 (0 %)	(0.0 ,0.0)	0.0079
Test	5	0 (0 %)	5 (100 %)	5 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Onychomycosis is considered as visit 4
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n = Number of subjects with the Onychomycosis scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 18: Analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by KOH smear for subjects with Onychomycosis (Per Protocol Population)

Treatment	KOH smear			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	5	0 (0 %)	0 (0 %)	0 (0 %)	(0.0 ,0.0)	0.0079
Test	5	0 (0 %)	5 (100 %)	5 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Onychomycosis is considered as visit 4
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n = Number of subjects with the Onychomycosis scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 19: Analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by KOH smear for subjects with Tinea and Onychomycosis (Per Protocol Population)

Treatment	KOH smear			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	14	0 (0 %)	0 (0 %)	0 (0 %)	(0.0 ,0.0)	<.0001
Test	14	0 (0 %)	13 (92.9 %)	13 (92.9 %)	(79.4 ,100.0)	

- End of study for the patients with Tinea is considered as visit 5 and patients with Onychomycosis is considered as visit 4
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n = Number of subjects with the Tinea scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 20: Summary of Fungal culture by visit for patients with Tinea (Modified Intention to treat Population)

VISIT	Test (N=9)				Placebo (N=9)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	9	100.00	0	0.00	9	100.00	0	0.00
End of study	0	0.00	9	100.00	5	55.56	4	44.44

Test=Biovite® Dermaceutical formulation (Cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects with Tinea
Source Listing: Tinea scrapings

Post Text Table 21: Summary of Fungal culture by visit for patients with Tinea (Per-Protocol Population)

VISIT	Test (N=9)				Placebo (N=9)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	9	100.00	0	0.00	9	100.00	0	0.00
End of study	0	0.00	9	100.00	5	55.56	4	44.44

Test=Biovite® Dermaceutical formulation (Cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects with Tinea
Source Listing: Tinea scrapings

Post Text Table 22: Summary of Fungal culture by visit for patients with Onychomycosis (Modified Intention to treat Population)

VISIT	Test (N=5)				Placebo (N=5)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	5	100.00	0	0.00	5	100.00	0	0.00
End of study	0	0.00	5	100.00	3	60.00	2	40.00

Test=Biovite® Dermaceutical formulation (lotion)
Placebo=Placebo formulation (lotion)
n/%=Number / percentage of patients with Onychomycosis
Source Listing: Onychomycosis scrapings

Post Text Table 23: Summary of Fungal culture by visit for patients with Onychomycosis (Per-Protocol Population)

VISIT	Test (N=5)				Placebo (N=5)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	5	100.00	0	0.00	5	100.00	0	0.00
End of study	0	0.00	5	100.00	3	60.00	2	40.00

Test=Biovite® Dermaceutical formulation (lotion)
Placebo=Placebo formulation (lotion)
n/%=Number / percentage of patients with Onychomycosis
Source Listing: Onychomycosis scrapings

Post Text Table 24: Summary of Fungal culture by visit for patients with Tinea and Onychomycosis (Per-Protocol Population)

VISIT	Test (N=14)				Placebo (N=14)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	14	100.00	0	0.00	14	100.00	0	0.00
End of study	0	0.00	14	100.00	8	57.14	6	42.86

Test=Biovite® Dermaceutical formulation (Cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects with Tinea
Source Listing: Tinea scrapings

Post Text Table 25: Analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by Fungal culture for subjects with Tinea (Modified Intention to treat Population)

Treatment	Fungal culture			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	9	0 (0 %)	4 (44.4 %)	4 (44.4 %)	(11.9 ,100.0)	0.0294
Test	9	0 (0 %)	9 (100 %)	9 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Tinea is considered as visit 5
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n = Number of subjects with the Tinea scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 26: Analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by Fungal culture for patients with Tinea (Per-Protocol Population)

Treatment	Fungal culture			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	9	0 (0 %)	4 (44.4 %)	4 (44.4 %)	(11.9 ,100.0)	0.0294
Test	9	0 (0 %)	9 (100 %)	9 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Tinea is considered as visit 5
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n = Number of subjects with the Tinea scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 27: Analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by Fungal culture smear for subjects with Onychomycosis (Modified Intention to treat Population)

Treatment	Fungal culture			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	5	0 (0 %)	2 (40 %)	2 (40 %)	(0.0 ,100.0)	0.1667
Test	5	0 (0 %)	5 (100 %)	5 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Onychomycosis is considered as visit 4
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n = Number of subjects with the Onychomycosis scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 28: Analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by Fungal culture smear for subjects with Onychomycosis (Per Protocol Population)

Treatment	**Fungal culture**			**Between Group Comparison**		
	n	**n (%) (Baseline)**	**n (%) (End of Study*)**	**Mycological cure n (%)**	**95% CI^**	**P-Value***
Placebo	5	0 (0 %)	2 (40 %)	2 (40 %)	(0.0 ,100.0)	0.1667
Test	5	0 (0 %)	5 (100 %)	5 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Onychomycosis is considered as visit 4
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n = Number of subjects with the Onychomycosis scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 29: Analysis of percentage of patients achieving mycological cure (negative response) from baseline at end of study as assessed by Fungal culture smear for subjects with Tinea and Onychomycosis (Per Protocol Population)

Treatment	Fungal culture			Between Group Comparison		
	n	p(%) (Baseline)	p(%) (End of Study*)	Mycological cure P(%)	95% CI^	P-Value*
Placebo	14	0 (0 %)	6 (42.9 %)	6 (42.9 %)	(17.0 ,100.0)	0.0019
Test	14	0 (0 %)	14 (100 %)	14 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Tinea is considered as visit 5 and patients with Onychomycosis is considered as visit 4
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n = Number of subjects with the Tinea scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 30: Summary of Spore counts by visit for patients with Tinea (Modified Intention to treat Population)

VISIT	Test (N=9)				Placebo (N=9)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	9	100.00	0	0.00	9	100.00	0	0.00
End of study	0	0.00	9	100.00	5	55.56	4	44.44

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of patients with Tinea
Source Listing: Tinea scrapings

Post Text Table 31: Summary of Spore counts by visit for patients with Tinea (Per-Protocol Population)

VISIT	Test (N=9)				Placebo (N=9)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	9	100.00	0	0.00	9	100.00	0	0.00
End of study	0	0.00	9	100.00	5	55.56	4	44.44

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of patients with Tinea
Source Listing: Tinea scrapings

Post Text Table 32: Summary of Spore counts by visit for patients with Onychomycosis (Modified Intention to treat Population)

VISIT	Test (N=5)				Placebo (N=5)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	5	100.00	0	0.00	5	100.00	0	0.00
End of study	0	0.00	5	100.00	3	60.00	2	40.00

Test=Biovite® Dermaceutical formulation (lotion)
Placebo=Placebo formulation (lotion)
n/%=Number / percentage of patients with Onychomycosis
Source Listing: Onychomycosis scrapings

Post Text Table 33: Summary of Spore counts by visit for patients with Onychomycosis (Per-Protocol Population)

VISIT	Test (N=5)				Placebo (N=5)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	5	100.00	0	0.00	5	100.00	0	0.00
End of study	0	0.00	5	100.00	3	60.00	2	40.00

Test=Biovite® Dermaceutical formulation (lotion)
Placebo=Placebo formulation (lotion)
n/%=Number / percentage of patients with Onychomycosis
Source Listing: Onychomycosis scrapings

Post Text Table 34: Summary of Spore counts by visit for patients with Tinea and Onychomycosis (Per-Protocol Population)

VISIT	Test (N=14)				Placebo (N=14)			
	Positive		Negative		Positive		Negative	
	n	%	n	%	n	%	n	%
Screening	14	100.00	0	0.00	14	100.00	0	0.00
End of study	0	0.00	14	100.00	8	57.14	6	42.86

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of patients with Tinea
Source Listing: Tinea scrapings

Post Text Table 35: Analysis of percentage of patients achieving mycological cure from baseline at end of study as assessed by Spore counts for patients with Tinea (Modified Intention to treat Population)

Treatment	Fungal culture			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	9	0 (0 %)	4 (44.4 %)	4 (44.4 %)	(11.9 ,100.0)	0.0294
Test	9	0 (0 %)	9 (100 %)	9 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Tinea is considered as visit 5
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n/p = Number/proportion of subjects with the Tinea scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 36: Analysis of percentage of patients achieving mycological cure from baseline at end of study as assessed by Spore counts for patients with Tinea (Per Protocol Population)

Treatment	Fungal culture			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	9	0 (0 %)	4 (44.4 %)	4 (44.4 %)	(11.9 ,100.0)	0.0294
Test	9	0 (0 %)	9 (100 %)	9 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Tinea is considered as visit 5
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n/p = Number/proportion of subjects with the Tinea scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 37: Analysis of percentage of patients achieving mycological cure from baseline at end of study as assessed by Spore counts for patients with Onychomycosis (Modified Intention to treat Population)

Treatment	Fungal culture			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	5	0 (0 %)	2 (40 %)	2 (40 %)	(0.0 ,100.0)	0.1667
Test	5	0 (0 %)	5 (100 %)	5 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Onychomycosis is considered as visit 4
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n/p = Number/proportion of subjects with the Onychomycosis scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 38: Analysis of percentage of patients achieving mycological cure from baseline at end of study as assessed by Spore counts for patients with Onychomycosis (Per Protocol Population)

Treatment	Fungal culture			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	5	0 (0 %)	2 (40 %)	2 (40 %)	(0.0 ,100.0)	0.1667
Test	5	0 (0 %)	5 (100 %)	5 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Onychomycosis is considered as visit 4
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n/p = Number/proportion of subjects with the Onychomycosis scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 39: Analysis of percentage of patients achieving mycological cure from baseline at end of study as assessed by Spore counts for patients with Tinea and Onychomycosis (Per Protocol Population)

Treatment	Fungal culture			Between Group Comparison		
	n	n (%) (Baseline)	n (%) (End of Study*)	Mycological cure n (%)	95% CI^	P-Value*
Placebo	14	0 (0 %)	6 (42.9 %)	6 (42.9 %)	(17.0 ,100.0)	0.0019
Test	14	0 (0 %)	14 (100 %)	14 (100 %)	(100.0 ,100.0)	

- End of study for the patients with Tinea is considered as visit 5 and patients with Onychomycosis is considered as visit 4
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
n/p = Number/proportion of patients with the Tinea/Onychomycosis scrapings test done
^ 95% CI is confidence interval from the proportions using binomial method. * P-value is from Fisher's exact test

Post Text Table 40: Summary of size of target lesion of Tinea by visit (Per-Protocol Population)

VISITS	Size of Tinea	Test (N=9)		Placebo (N=9)	
		n	%	n	%
VISIT 1	6	1	11.11	1	11.11
	7	0	0.00	3	33.33
	8	2	22.22	2	22.22
	9	0	0.00	1	11.11
	10	0	0.00	2	22.22
	12	1	11.11	0	0.00
	15	2	22.22	0	0.00
	18	2	22.22	0	0.00
	20	1	11.11	0	0.00
VISIT 2	5	2	22.22	1	11.11
	6	1	11.11	2	22.22
	7	0	0.00	3	33.33
	8	1	11.11	1	11.11
	9	0	0.00	2	22.22
	12	3	33.33	0	0.00
	14	1	11.11	0	0.00
	16	1	11.11	0	0.00
VISIT 3	3	2	22.22	0	0.00
	4	1	11.11	0	0.00
	6	1	11.11	1	11.11
	7	1	11.11	4	44.44
	8	0	0.00	2	22.22
	9	1	11.11	1	11.11
	10	3	33.33	1	11.11
VISIT 4	2	3	33.33	0	0.00
	4	1	11.11	0	0.00
	5	1	11.11	0	0.00
	6	2	22.22	2	22.22
	7	1	11.11	3	33.33
	8	1	11.11	2	22.22
	9	0	0.00	1	11.11
	11	0	0.00	1	11.11
VISIT 5	1	2	22.22	0	0.00
	2	1	11.11	0	0.00
	3	3	33.33	0	0.00
	4	2	22.22	0	0.00
	5	0	0.00	2	22.22
	6	0	0.00	1	11.11

VISITS	Size of Tinea	Test (N=9)		Placebo (N=9)	
		n	%	n	%
	7	1	11.11	1	11.11
	8	0	0.00	2	22.22
	12	0	0.00	1	11.11
	13	0	0.00	1	11.11
	15	0	0.00	1	11.11

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects reporting the extent score
Source Listing: Tinea assessment

Post Text Table 41: Analysis of change from baseline at End of study in Size of Tinea in target lesion (Per-Protocol Population)

Treatment .	N .	Mean (SD)			Between-group comparisons (Test-Placebo)		
		Baseline visit	End of study visit	Change§	Mean Difference †	95% C.I.	P-value*
Test	9	13.3 (5.1)	3.1 (1.8)	-10.2 (3.7)	-11.0	(-14.47, -7.53)	<.0001
Placebo	9	8.0 (1.4)	8.8 (3.7)	0.8 (3.2)			

Test=Biovite® Dermaceutical formulation (cream), Placebo=Placebo formulation (cream)
§ Change = size at visit 5 - size at baseline visit
† Difference = between-group difference in change from baseline visit
P-value*: P-value from two sample t test for change, 95% CI: 95% confidence interval from ttest procedure
Source listing: Tinea assessment

Post Text Table 42: Summary of severity score of target lesion of Tinea by visit (Per-Protocol Population)

VISITS	Severity score	Test (N=9)		Placebo (N=9)	
		n	%	n	%
VISIT 1	8	1	11.11	2	22.22
	9	7	77.78	6	66.67
	10	1	11.11	1	11.11
VISIT 2	5	1	11.11	0	0.00
	6	3	33.33	0	0.00
	7	4	44.44	0	0.00
	8	1	11.11	5	55.56
	9	0	0.00	4	44.44
VISIT 3	4	1	11.11	0	0.00
	5	4	44.44	0	0.00
	6	4	44.44	0	0.00
	7	0	0.00	1	11.11

VISITS	Severity score	Test (N=9)		Placebo (N=9)	
		n	%	n	%
	8	0	0.00	4	44.44
	9	0	0.00	4	44.44
VISIT 4	2	1	11.11	0	0.00
	3	3	33.33	0	0.00
	4	3	33.33	0	0.00
	5	1	11.11	0	0.00
	6	1	11.11	1	11.11
	8	0	0.00	5	55.56
	9	0	0.00	3	33.33
VISIT 5	1	1	11.11	0	0.00
	2	4	44.44	0	0.00
	3	3	33.33	0	0.00
	4	1	11.11	0	0.00
	6	0	0.00	3	33.33
	8	0	0.00	2	22.22
	9	0	0.00	1	11.11
	10	0	0.00	3	33.33

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects reporting the severity score
Source Listing: Tinea assessment

Post Text Table 43: Analysis of change from baseline at End of study in severity score of Tinea in target lesion (Per-Protocol Population)

Treatment .	N .	Mean (SD)			Between-group comparisons (Test-Placebo)		
		Baseline visit	End of study visit	Change§	Mean Difference †	95% C.I.	P-value*
Test	9	9.0 (0.5)	2.4 (0.9)	-6.6 (0.5)	-5.78	(-7.32, -4.23)	<.0001
Placebo	9	8.9 (0.6)	8.1 (1.8)	-0.8 (2.0)			

Test=Biovite® Dermaceutical formulation (cream), Placebo=Placebo formulation (cream)
§ Change = size at visit 5 - size at baseline visit
† Difference = between-group difference in change from baseline visit
P-value*: P-value from two sample t test for change, 95% CI: 95% confidence interval from ttest procedure
Source listing: Tinea assessment

Post Text Table 44: Percentage of surface area involved by visit (Per-Protocol Population)

VISITS	%Surface area	Test (N=5)		Placebo (N=5)	
		n	%	n	%
VISIT 1	60	3	60.00	2	40.00
	65	1	20.00	0	0.00
	70	1	20.00	3	60.00
VISIT 2	50	3	60.00	1	20.00
	55	1	20.00	1	20.00
	60	1	20.00	3	60.00
VISIT 3	30	1	20.00	0	0.00
	40	3	60.00	0	0.00
	50	0	0.00	2	40.00
	55	0	0.00	2	40.00
	60	1	20.00	1	20.00
VISIT 4	20	1	20.00	0	0.00
	25	1	20.00	0	0.00
	30	2	40.00	0	0.00
	40	1	20.00	0	0.00
	50	0	0.00	4	80.00
	55	0	0.00	1	20.00
VISIT 5	20	2	40.00	0	0.00
	25	1	20.00	0	0.00
	30	2	40.00	0	0.00
	50	0	0.00	4	80.00
	55	0	0.00	1	20.00
VISIT 6	15	2	40.00	0	0.00
	20	1	20.00	0	0.00
	25	2	40.00	0	0.00
	50	0	0.00	2	40.00
	55	0	0.00	3	60.00
VISIT 7	10	1	20.00	0	0.00
	15	1	20.00	0	0.00
	20	2	40.00	0	0.00
	25	1	20.00	0	0.00
	45	0	0.00	1	20.00
	50	0	0.00	2	40.00
	55	0	0.00	2	40.00

Test=Biovite® Dermaceutical formulation (lotion)
Placebo=Placebo formulation (lotion)
n/%=Number / percentage of subjects reporting the %Surface area
Source Listing: Onychomycosis assessment

Post Text Table 45: Analysis of change from baseline at End of study in Percentage of surface area involved in Onychomycosis (Per-Protocol Population)

Treatment.	N.	Mean (SD)			Between-group comparisons (Test-Placebo)		
		Baseline visit	End of study visit	Change§	Mean Difference †	95% C.I.	P-value*
Test	5	63.0 (4.5)	18.0 (5.7)	-45.0 (5.0)	-30.0	(-39.65, -20.35)	<.0001
Placebo	5	66.0 (5.5)	51.0 (4.2)	-15.0 (7.9)			

Test=Biovite® Dermaceutical formulation (lotion), Placebo=Placebo formulation (lotion)
§ Change = size at visit 5 - size at baseline visit
† Difference = between-group difference in change from baseline visit
P-value*: P-value from two sample t test for change, 95% CI: 95% confidence interval from ttest procedure
Source listing: Onychomycosis assessment

Post Text Table 46: Summary of extent and severity score of target lesion of Onychomycosis by visit (Per-Protocol Population)

VISITS	Extent and severity score	Test (N=5)		Placebo (N=5)	
		n	%	n	%
VISIT 1	3	5	100.00	5	100.00
VISIT 2	2	4	80.00	1	20.00
	3	1	20.00	4	80.00
VISIT 3	2	5	100.00	1	20.00
	3	0	0.00	4	80.00
VISIT 4	1	5	100.00	0	0.00
	2	0	0.00	1	20.00
	3	0	0.00	4	80.00
VISIT 5	1	4	80.00	0	0.00
	2	0	0.00	1	20.00
	3	1	20.00	4	80.00
VISIT 6	1	5	100.00	0	0.00
	2	0	0.00	1	20.00
	3	0	0.00	4	80.00
VISIT 7	1	5	100.00	0	0.00
	2	0	0.00	1	20.00
	3	0	0.00	4	80.00

Test=Biovite® Dermaceutical formulation (lotion)
Placebo=Placebo formulation (lotion)
n/%=Number / percentage of subjects reporting the extent and severity score
Source Listing: Onychomycosis assessment

Post Text Table 47: Analysis of change from baseline at End of study in extent and severity score of target lesion of Onychomycosis (Per-Protocol Population)

Treatment .	N .	Mean (SD)			Between-group comparisons (Test-Placebo)		
		Baseline visit	End of study visit	Change§	Mean Difference †	95% C.I.	P-value*
Test	5	3.0 (0.0)	1.0 (0.0)	-2.0 (0.0)	-1.8	(-2.36, -1.24)	.0008
Placebo	5	3.0 (0.0)	2.8 (0.4)	-0.2 (0.4)			

Test=Biovite® Dermaceutical formulation (lotion), Placebo=Placebo formulation (lotion)
§ Change = size at visit 5 - size at baseline visit
† Difference = between-group difference in change from baseline visit
P-value*: P-value from two sample t test for change, 95% CI: 95% confidence interval from ttest procedure
Source listing: Onychomycosis assessment

Post Text Table 48: Summary of investigator global assessment response of cleared or excellent by visit for patients with Tinea (Per-Protocol Population)

VISITS	Test (N=9)				Placebo (N=9)			
	Cleared		Excellent		Cleared		Excellent	
	n	%	n	%	n	%	n	%
VISIT 2	1	11.11	0	0.00	0	0.00	0	0.00
VISIT 3	9	100.00	0	0.00	0	0.00	0	0.00
VISIT 4	7	77.78	2	22.22	0	0.00	0	0.00
VISIT 5	3	33.33	6	66.67	0	0.00	0	0.00

Test=Biovite® Dermaceutical formulation (cream)
Placebo=Placebo formulation (cream)
n/%=Number / percentage of subjects in 'Cleared' or 'Excellent' category as assessed by the investigator
Source Listing: Physician assessment of treatment response

Post Text Table 49: Summary of investigator global assessment response of cleared or excellent by visit for patients with Onychomycosis (Per-Protocol Population)

VISITS	Test (N=5)				Placebo (N=5)			
	Cleared		Excellent		Cleared		Excellent	
	n	%	n	%	n	%	n	%
VISIT 3	2	40.00	0	0.00	0	0.00	0	0.00
VISIT 4	3	60.00	2	40.00	0	0.00	0	0.00
VISIT 5	3	60.00	2	40.00	0	0.00	0	0.00
VISIT 6	0	0.00	5	100.00	0	0.00	0	0.00
VISIT 7	0	0.00	5	100.00	0	0.00	0	0.00

Test=Biovite® Dermaceutical formulation (lotion)
Placebo=Placebo formulation (lotion)
n/%=Number / percentage of subjects in 'Cleared' or 'Excellent' category as assessed by the investigator
Source Listing: Physician assessment of treatment response

Post Text Table 50: Summary of investigator global assessment response of cleared or excellent by visit for subjects with Tinea and Onychomycosis (Per-Protocol Population)

VISITS	Test (N=14)				Placebo (N=14)			
	Cleared		Excellent		Cleared		Excellent	
	n	%	n	%	n	%	n	%
VISIT 2	1	7.14	0	0.00	0	0.00	0	0.00
VISIT 3	11	78.57	0	0.00	0	0.00	0	0.00
VISIT 4	10	71.43	4	28.57	0	0.00	0	0.00
VISIT 5	6	42.86	8	57.14	0	0.00	0	0.00
VISIT 6	0	0.00	5	35.71	0	0.00	0	0.00
VISIT 7	0	0.00	5	35.71	0	0.00	0	0.00

Test=Biovite® Dermaceutical formulation (cream)

Placebo=Placebo formulation (cream) n/%=Number / percentage of subjects in 'Cleared' or 'Excellent' category as assessed by the investigator Source Listing: Physician assessment of treatment response

Post Text Table 51: Summary of Improvement in lesions assessed by photographic record at baseline and at end of study Tinea (Per-Protocol Population)

Test (N=9)				Placebo (N=9)			
No		Yes		No		Yes	
n	%	n	%	n	%	n	%
0	0.00	9	100.00	9	100.00	0	0.00
Test=Biovite® Dermaceutical formulation (cream) Placebo=Placebo formulation (cream) n/%=Number / percentage of patients in 'Yes' or 'No' category as assessed by the investigator for photographic record Source Listing: Physician assessment of treatment response							

Post Text Table 52: Summary of Improvement in lesions assessed by photographic record at baseline and at end of study for Onychomycosis (Per-Protocol Population)

Test (N=5)				Placebo (N=5)			
No		Yes		No		Yes	
n	%	n	%	n	%	n	%
0	0.00	5	100.00	5	100.00	0	0.00
Test=Biovite® Dermaceutical formulation (lotion) Placebo=Placebo formulation (lotion) n/%=Number / percentage of patients in 'Yes' or 'No' category as assessed by the investigator for photographic record Source Listing: Physician assessment of treatment response							

Post Text Table 53: Summary of Improvement in lesions assessed by photographic record at baseline and at end of study Tinea or Onychomycosis (Per-Protocol Population)

Test (N=14)				Placebo (N=14)			
No		Yes		No		Yes	
n	%	n	%	n	%	n	%
0	0.00	14	100.00	14	100.00	0	0.00
Test=Biovite® Dermaceutical formulation (cream) Placebo=Placebo formulation (cream) n/%=Number / percentage of subjects in 'Yes' or 'No' category as assessed by the investigator for photographic record Source Listing: Physician assessment of treatment response							

14.3 SAFETY DATA

14.3.1 Displays of Adverse Events

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

There were no deaths, other serious and significant AEs reported in this study.

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant AEs

Not Applicable

14.3.4 Abnormal Laboratory Value Listing (Each Patient)

Not applicable

14.3.5 Vital Signs

Post Text Table 54: Summary of vital signs by visit (Safety Population)

Vital Signs	Visit	Summary statistics	Test	Placebo
Systolic BP (mmHg)	Visit 1	N	14	14
		Mean	124.1	127.3
		SD	6.86	4.48
		Minimum	110.0	118.0
		Median	126.0	130.0
		Maximum	132.0	132.0
	Visit 2	N	14	14
		Mean	124.1	126.6
		SD	4.26	4.11
		Minimum	114.0	120.0
		Median	125.0	128.0
		Maximum	128.0	134.0
	Visit 3	N	14	14
		Mean	122.7	125.7
		SD	5.53	3.58
		Minimum	110.0	118.0
		Median	124.0	127.0
		Maximum	132.0	130.0
	Visit 4	N	14	14
		Mean	123.4	125.7
		SD	5.68	2.81

Vital Signs	Visit	Summary statistics	Test	Placebo
		Minimum	114.0	120.0
		Median	124.0	126.0
		Maximum	134.0	132.0
	Visit 5*	N	14	14
		Mean	124.6	126.6
		SD	5.52	4.03
		Minimum	114.0	120.0
		Median	126.0	127.0
		Maximum	132.0	134.0
	Visit 6	N	5	5
		Mean	122.4	125.6
		SD	3.29	3.85
		Minimum	120.0	120.0
		Median	120.0	126.0
		Maximum	126.0	130.0
	Visit 7*	N	5	5
		Mean	122.4	125.6
		SD	6.99	4.56
		Minimum	114.0	118.0
		Median	122.0	126.0
		Maximum	132.0	130.0
Diastolic BP (mmHg)	Visit 1	N	14	14
		Mean	79.7	82.3
		SD	4.83	2.58
		Minimum	70.0	76.0
		Median	82.0	83.0
		Maximum	84.0	86.0
	Visit 2	N	14	14
		Mean	80.4	82.0
		SD	4.24	2.08
		Minimum	72.0	78.0
		Median	82.0	82.0
		Maximum	84.0	84.0
	Visit 3	N	14	14
		Mean	80.6	82.0
		SD	3.54	2.22
		Minimum	72.0	78.0
		Median	82.0	82.0
		Maximum	84.0	86.0
	Visit 4	N	14	14

Vital Signs	Visit	Summary statistics	Test	Placebo
		Mean	80.1	82.7
		SD	2.98	1.49
		Minimum	74.0	80.0
		Median	81.0	82.0
		Maximum	84.0	86.0
	Visit 5*	N	14	14
		Mean	81.3	82.4
		SD	3.47	2.85
		Minimum	72.0	74.0
		Median	82.0	83.0
		Maximum	84.0	86.0
	Visit 6	N	5	5
		Mean	79.6	82.0
		SD	4.77	3.46
		Minimum	74.0	76.0
		Median	80.0	84.0
		Maximum	86.0	84.0
	Visit 7*	N	5	5
		Mean	80.8	82.4
		SD	5.40	3.58
		Minimum	74.0	76.0
		Median	84.0	84.0
		Maximum	86.0	84.0
Heart rate (beats/min)	Visit 1	N	14	14
		Mean	69.3	69.6
		SD	1.86	1.34
		Minimum	68.0	66.0
		Median	68.0	70.0
		Maximum	74.0	72.0
	Visit 2	N	14	14
		Mean	70.8	70.3
		SD	2.22	2.20
		Minimum	68.0	68.0
		Median	70.0	70.0
		Maximum	76.0	74.0
	Visit 3	N	14	14
		Mean	70.4	70.1
		SD	1.95	2.11
		Minimum	68.0	68.0
		Median	70.0	70.0

Vital Signs	Visit	Summary statistics	Test	Placebo
		Maximum	74.0	76.0
	Visit 4	N	14	14
		Mean	70.4	71.0
		SD	1.65	2.18
		Minimum	68.0	68.0
		Median	70.0	70.0
		Maximum	74.0	74.0
	Visit 5*	N	14	14
		Mean	70.3	69.6
		SD	2.37	1.55
		Minimum	67.0	68.0
		Median	70.0	70.0
		Maximum	76.0	72.0
	Visit 6	N	5	5
		Mean	71.2	71.2
		SD	3.63	1.79
		Minimum	68.0	70.0
		Median	70.0	70.0
		Maximum	76.0	74.0
	Visit 7*	N	5	5
		Mean	72.2	72.4
		SD	2.05	1.67
		Minimum	69.0	70.0
		Median	72.0	72.0
		Maximum	74.0	74.0
Temperature (°F)	Visit 1	N	14	14
		Mean	98.2	98.3
		SD	0.09	0.10
		Minimum	98.2	98.2
		Median	98.2	98.2
		Maximum	98.4	98.4
	Visit 2	N	14	14
		Mean	98.2	98.2
		SD	0.07	0.09
		Minimum	98.2	98.2
		Median	98.2	98.2
		Maximum	98.4	98.4
	Visit 3	N	14	14
		Mean	98.2	98.3
		SD	0.07	0.10

Vital Signs	Visit	Summary statistics	Test	Placebo
		Minimum	98.2	98.2
		Median	98.2	98.2
		Maximum	98.4	98.4
	Visit 4	N	14	14
		Mean	98.3	98.3
		SD	0.09	0.09
		Minimum	98.2	98.2
		Median	98.2	98.2
		Maximum	98.4	98.4
	Visit 5*	N	14	14
		Mean	98.3	98.3
		SD	0.10	0.10
		Minimum	98.2	98.2
		Median	98.2	98.2
		Maximum	98.4	98.4
	Visit 6	N	5	5
		Mean	98.2	98.2
		SD	0.09	0.00
		Minimum	98.2	98.2
		Median	98.2	98.2
		Maximum	98.4	98.2
	Visit 7*	N	5	5
		Mean	98.2	98.2
		SD	0.00	0.09
		Minimum	98.2	98.2
		Median	98.2	98.2
		Maximum	98.2	98.4
Respiratory rate (breaths/min)	Visit 1	N	14	14
		Mean	13.5	13.6
		SD	0.65	0.50
		Minimum	13.0	13.0
		Median	13.0	14.0
		Maximum	15.0	14.0
	Visit 2	N	14	14
		Mean	13.7	13.5
		SD	0.73	0.76
		Minimum	13.0	13.0
		Median	14.0	13.0
		Maximum	15.0	15.0
	Visit 3	N	14	14

Vital Signs	Visit	Summary statistics	Test	Placebo
		Mean	13.6	13.5
		SD	0.74	0.52
		Minimum	12.0	13.0
		Median	14.0	13.5
		Maximum	15.0	14.0
	Visit 4	N	14	14
		Mean	13.7	14.1
		SD	1.14	0.62
		Minimum	12.0	13.0
		Median	13.0	14.0
		Maximum	16.0	15.0
	Visit 5*	N	14	14
		Mean	13.6	13.8
		SD	0.76	0.70
		Minimum	12.0	13.0
		Median	14.0	14.0
		Maximum	15.0	15.0
	Visit 6	N	5	5
		Mean	15.2	14.8
		SD	0.84	0.45
		Minimum	14.0	14.0
		Median	15.0	15.0
		Maximum	16.0	15.0
	Visit 7*	N	5	5
		Mean	14.6	14.8
		SD	0.55	0.84
		Minimum	14.0	14.0
		Median	15.0	15.0
		Maximum	15.0	16.0

# = Visit 5 is the end of study for patients with Tinea and Visit 7 for patients with Onychomycosis
Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
Source Listing: Vital Signs

Post Text Table 55: Summary of Change from screening visit in vital signs by visit (Safety Population)

Vital Signs		Visit	Summary statistics	Test	Placebo
Tinea	Systolic BP (mmHg)	Change from visit 1 to Visit 5	N	9	9

Vital Signs		Visit	Summary statistics	Test	Placebo
			Mean	0.9	-1.1
			SD	9.23	6.09
			Minimum	-12.0	-10.0
			Median	0.0	-4.0
			Maximum	22.0	10.0
	Diastolic BP (mmHg)		N	9	9
			Mean	2.2	0.7
			SD	3.80	2.45
			Minimum	-2.0	-4.0
			Median	0.0	2.0
			Maximum	10.0	4.0
	Heart rate (beats/min)		N	9	9
			Mean	0.2	0.4
			SD	2.28	2.24
			Minimum	-2.0	-2.0
			Median	0.0	0.0
			Maximum	6.0	6.0
	Temperature (°F)		N	9	9
			Mean	0.0	0.0
			SD	0.12	0.17
			Minimum	-0.2	-0.2
			Median	0.0	0.0
			Maximum	0.2	0.2
	Respiratory rate (breaths/min)		N	9	9
			Mean	-0.3	-0.3
			SD	0.50	0.50
			Minimum	-1.0	-1.0
			Median	0.0	0.0
			Maximum	0.0	0.0
Onychomycosis	Systolic BP (mmHg)	Change from visit 1 to Visit 4	N	5	5
			Mean	0.8	-1.2
			SD	3.90	1.79
			Minimum	-4.0	-4.0
			Median	2.0	0.0
			Maximum	6.0	0.0
	Diastolic BP (mmHg)		N	5	5
			Mean	2.8	1.2
			SD	3.35	1.79

Vital Signs		Visit	Summary statistics	Test	Placebo
			Minimum	0.0	0.0
			Median	2.0	0.0
			Maximum	8.0	4.0
	Heart rate (beats/min)		N	5	5
			Mean	3.8	2.6
			SD	1.79	1.95
			Minimum	1.0	0.0
			Median	4.0	2.0
			Maximum	6.0	5.0
	Temperature (°F)		N	5	5
			Mean	-0.0	-0.0
			SD	0.09	0.17
			Minimum	-0.2	-0.2
			Median	0.0	0.0
			Maximum	0.0	0.2
	Respiratory rate (breaths/min)		N	5	5
			Mean	1.4	1.4
			SD	0.55	0.89
			Minimum	1.0	1.0
			Median	1.0	1.0
			Maximum	2.0	3.0

Test=Biovite® Dermaceutical formulation (cream & lotion)
Placebo=Placebo formulation (cream & lotion)
Source Listing: Vital Signs

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16 APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol and protocol amendments
16.1.2 Sample case report form
16.1.3 List of IECs or IRBs and sample ICFs
16.1.3.1 List of EC members and EC approval letter
16.1.3.2 Sample ICFs in 4 languages
16.1.4 List and description of investigators and other important participants in the study, including brief CVs or equivalent summaries of training and experience relevant to the performance of the clinical study
16.1.5 Signature of principal or coordinating investigator(s) or sponsor's responsible medical officer.
16.1.6 Listing of patients receiving test/reference product(s) from specific batches, when more than one batch was used
16.1.7 Randomization scheme and codes (patient identification and treatment assigned)
16.1.8 Quality assurance statement
16.1.9 Documentation of statistical methods
16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used
- Not applicable
16.1.11 Publications based on study
- Not Applicable
16.1.12 Important publications referenced in the report
- Not Available

16.2 PATIENT DATA LISTINGS

16.2.1 Discontinued Subjects
16.2.2 Protocol Deviation
16.2.3 Listing of Patients Excluded From Efficacy Analysis
16.2.4 Demographic Data
16.2.5 Individual Efficacy Response Data
16.2.6 Study Medication Accountability
16.2.7 Adverse Events
16.2.8 Lab Fungus Culture
16.2.8.1 Lab Live Spore Count
16.2.9 Diagnosis of Onychomycosis
16.2.10 Onychomycosis Assessment
16.2.11 Onychomycosis Scrapings
16.2.12 Onychomycosis Photographic Assessment
16.2.13 Tinea Assessment
16.2.14 Tinea Scrapings
16.2.15 Physical Examination
16.2.16 Physician Assessment

16.2.17 Patient Diary Card
16.2.18 Informed Consent
16.2.19 Inclusion Criteria
16.2.20 Investigator's Statement
16.2.21 Vital Signs
16.2.22 Medical History
16.2.23 Unscheduled Visit
16.2.24 Date of Visit
16.2.25 Concomitant Medication
16.2.26 Screening Failure
16.2.27 Randomization
16.2.28 End of Study
16.2.29 Comments
16.2.30 Serious Adverse Events
16.2.31 Compliance

16.3 CASE REPORT FORMS

16.3.1 CRF's of deaths, other SAEs and withdrawals due to AE
Not Applicable
16.3.2 Other CRF's submitted
Not Applicable