The Effect of Riboflavin on Moderate to Severe Plaque Type Psoriasis

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1 SYNOPSIS

The purpose of this investigation is to determine the anti-inflammatory effect of high-dose riboflavin supplementation on chronic plaque psoriasis. Up to fifty volunteers with chronic plaque psoriasis will be recruited for a double-blind, placebo-controlled 28 week prospective study with cross-over of both the intervention and control groups at the 12 week time mark. There will be a 4 week washout period when subjects crossover. Riboflavin will be dosed 400 mg by mouth daily versus placebo. Throughout the study we will perform both clinical and laboratory assessments to measure response. Clinical assessment will include the Psoriasis-Area-and-Severity-Index (PASI), Physician Global Assessment (PGA), Dermatology -Life-Quality-Index (DLQI) and pruritus assessment will be performed at all clinical evaluations. Photographs of volunteers' skin will be taken. Skin punch biopsies of psoriasis plaques and uninvolved skin will be performed at pre-determined time points throughout the study to measure metabolomics and RNA profiling as well as histologic markers. Patients will also have regular blood draws to follow plasma measurements of riboflavin and Flavin-adenine-dinucleotide (FAD).

The primary objective is to demonstrate the superiority of riboflavin as compared to placebo at achieving a PASI 50 response (a 50% or greater improvement in PASI from baseline). Secondary objectives include, measuring the efficacy of the intervention at achieving a PGA, DLQI, or pruritus assessment score of 0/1. All statistics will be performed on a modified intent-to-treat population.

2 BACKGROUND

Psoriasis is a chronic immune-mediated skin disorder characterized by complex alterations in epidermal growth and differentiation with multiple biochemical and immunologic abnormalities. Characteristic lesions are well-demarcated, symmetrically distributed red plaques with silvery scale. In the United States, the prevalence of psoriasis is estimated to be 2% and it affects over 4 million people. [1,2] Psoriasis patients suffer from reduced quality of life related to the discomfort, social stigma, and disability caused by their disease.[2] The overall economic burden of psoriasis on the United States was recently estimated at 35.2 billion dollars with 12.2 billion dollars attributed to incremental medical costs and the rest from productivity and health-related quality of life losses.[2] There is no cure for psoriasis and treatment is directed at controlling patients' symptoms. Current treatment options consist of topical steroids, phototherapy, topical vitamin D3 (or calcipotriol), methotrexate, and newer biologic agents.

Amongst patients with skin disease, there is significant interest in using complementary alternative medicine and vitamins to treat their disease.[3] Some of this interest is driven by the proven efficacy of calcipotriol ointment for the treatment of psoriasis. Randomized controlled trials have shown topical calcipotriol ointment to be equivalent to a Class V topical steroid and that it has an excellent safety profile.[4-6] This efficacy and safety led the United States Food and Drug Administration to approve calcipotriol ointment for psoriasis treatment in 1993 and since that time it has been an important part of psoriasis treatment.

Given this interest in vitamin treatments and the proven efficacy of vitamin treatment for psoriasis we were intrigued when our laboratory work uncovered a significant decrease in riboflavin levels in psoriasis plaques. While measuring the metabolic profile of psoriasis plaques as compared to skin from healthy volunteers, we measured 400 fold less riboflavin in psoriatic plaques (Gudjonsson, unpublished findings). Furthermore, exploring predicted drug targets using recent Genome-Wide-Association-Studies (GWAS) in psoriasis, two risk loci (*ACOX1* and *NOS2*) are targets of flavin-adenine-dinucleotide (FAD) a metabolite of riboflavin. Reviewing the medical literature, we found a number of case series from fifty to sixty years ago reporting improvement of psoriasis after riboflavin treatment.[7-9] Our laboratory findings and these case reports prompted our interest in exploring the use of this vitamin to treat psoriasis.

Riboflavin, commonly known as Vitamin B2, is a water-soluble vitamin found in all living cells as mono- or dinucleotides. It is part of the Flavin family of compounds, and is the necessary precursor of the biologically important flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN).[10] While plants and many microorganisms may generate riboflavin *de novo*, animals rely on dietary sources that they then convert to FAD and FMN.[11] In human diets, major sources include dairy products, eggs, grains, and green leafy vegetables.[12] Once consumed, riboflavin is absorbed via a carrier-mediated mechanism in the proximal small intestine and then excreted in the urine.[12] Riboflavin is not stored in the body making a constant dietary supply necessary. Worldwide, Riboflavin is a bulk commodity with about 3,000 metric tons produced per year.[10] A majority of this production is directed towards animal husbandry with a minority used for human food supplementation.[10]

The clinical effects of riboflavin supplementation on psoriasis were first explored in the 1950s. In 1952, Dr. Maynard published a case series of 148 psoriasis patients he had injected with 5-10 mg of riboflavin intramuscularly once weekly and then followed clinically. Of those 148 patients, 24% had complete remission ("healed"), and 68% had at least a 50% improvement. Only 7% of the patients failed to respond or had less than a 50% improvement. Maynard also sent surveys to 156 of his psoriasis patients that he had treated with riboflavin but whom he had not seen in clinic for two years. He received 50 survey cards back and, of those cards, 82% of patients reported they had "healed," "improved with no relapse," or "improved with partial relapse." Only 18% of responders felt their disease was the same as before riboflavin treatment.[7]

Maynard's work was soon followed by other publications on the topic. In 1952, Sulzberger and Baer published their observations that riboflavin 30 mg by mouth daily did not help psoriasis.[8] In contrast, in 1954, Italian investigators Montilli and Pisani reported that daily intramuscular injections of 10 mg of riboflavin either clinically cured or improved the disease in 33 out of 42 psoriasis.[8] In 1956, Dr. Herbert Luscombe published a case series demonstrating that weekly intramuscular injections of 50 mg of riboflavin for 4 to 16 weeks "improved" or "markedly improved" 39 out of 44 psoriatic patients in his clinic.[9] In contrast, in 1957, Drs. Welsh and Ede published a large case series of 348 psoriasis patients they treated with riboflavin and concluded "moderate and/or massive dosages" of riboflavin

failed to produce any significant response in those patients.[8] To our knowledge, there have been no more published trials or case series on the clinical effects of treating psoriasis with riboflavin. Taken together we think the results of these trials are intriguing and create clinical equipoise on whether riboflavin is an effective treatment for psoriasis.

While publications examining riboflavin and psoriasis largely stopped after the 1950s, neurologists became interested in whether riboflavin could be used to treat migraines in the 1990s. We found three human trials published on the clinical effects of riboflavin on migraine headaches involving 152 human subjects. Two of these publications included the results from randomized controlled trials and the third was an open-label study. In these reports, subjects were followed for three to six months and all subjects in the intervention groups were administered riboflavin 400 mg by mouth daily either blinded or open-label - 75 subjects total. Two of the studies observed a statistically significant and clinically meaningful improvement in the number of migraine attacks.[13,14] The third study observed a statistically significant placebo effect and so found no benefit to the intervention. Interestingly, the blinded placebo in this randomized controlled trial was riboflavin 25 mg by mouth daily, so the authors wondered if even this low dose of riboflavin was biologically active. This trial was stopped prematurely, because interim analysis demonstrated the intervention would not show a statistically significant result. The authors were unable to conclude whether the results with the lower-dose of riboflavin (the "placebo group") were an active effect or a placebo effect.[15]

Riboflavin was well tolerated by the subjects in these studies. Only two publications included data on adverse outcomes associated with riboflavin and within these trials there were five adverse events out of the 51 patients administered riboflavin. Adverse events included diarrhea (2 subjects), upper abdominal pain, facial erythema and polyuria.[13,14] One subject who experienced diarrhea withdrew early from the trial but it was reported that her symptoms resolved within 72 hours.[13] Both studies concluded that riboflavin was safe and well-tolerated.

Finally, in ophthalmology, photoactivated riboflavin has been used for the last twelve years to treat structural deformities and inflammatory conditions of the cornea such as, keratoconus, keratectasia, and infectious keratitis.[16-18] In this technique the corneal epithelium is removed, riboflavin is applied and the tissue is irradiated with ultraviolet A light.[17] The riboflavin strengthens the collagen in the cornea and biochemically stabilizes the layer to prevent further complications from these conditions.[16,17]

In conclusion, psoriasis is a common and socially stigmatizing condition in the United States. Our laboratory metabolomics profiling has shown that psoriasis plaques have significantly less riboflavin than healthy controls. Previous human case reports suggest that riboflavin is clinically effective for the treatment of psoriasis; however, they were not conclusive. More recent human trials have shown that 400 mg of daily oral riboflavin is a safe and well-tolerated medication to administer to humans. Our laboratory data, the published case reports of riboflavin's effectiveness and its safety led us to propose these clinical and laboratory experiments to better determine riboflavin's effects on psoriasis.

3 OBJECTIVES

3.1 Primary endpoint

The number of subjects that achieve a 50 percent or greater reduction in their PASI with intervention as compared to placebo.

3.2 Secondary endpoints

- The number of subjects that achieve a PASI 75, 90, 100 response with intervention as compared to placebo.
- The number of subjects that achieve a PGA score of 0/1 with intervention as compared to placebo.
- The number of subjects that report a pruritus score of 0/1 with intervention as compared to placebo.
- The number of subjects treated that report a DLQI score of 0/1 with intervention as compared to placebo.
- The difference in serum plasma levels of riboflavin and FAD in subjects treated with intervention as compared to placebo.

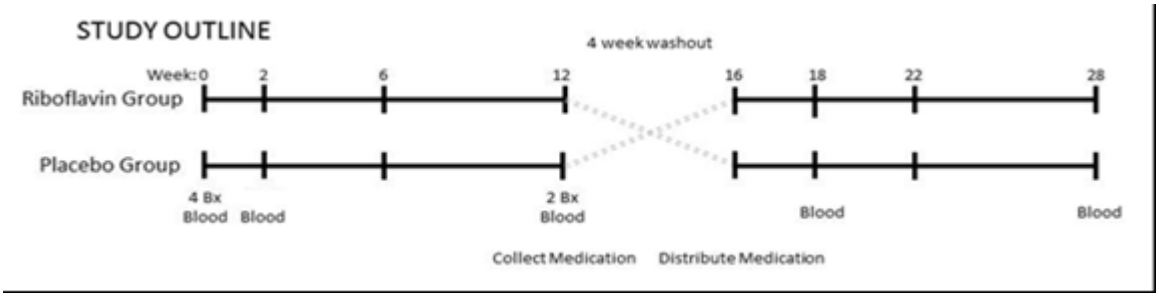
4 STUDY DESIGN

A 28-week, double-blind, placebo-controlled, prospective study with cross-over of both the riboflavin and placebo groups at the 12-week time mark.

Patients will take either 400 mg of riboflavin ("B2-400") or a placebo by mouth once a day for 12 weeks. There will be a four week wash-out period at week 12 as the groups cross-over.

We propose using a 400 mg daily dose in this clinical trial as there is the most evidence in previous human studies for a clinical effect with this dose. While data suggesting equivalent activity of riboflavin at a lower dose is intriguing, we feel it is premature to choose a lower dose based off the findings in one trial that was stopped prematurely.[15]

Up to 50 subjects will be enrolled. Six skin biopsies will be performed to measure metabolomics profiles, and there will be five blood draws to measure serologic markers.



5 INVESTIGATIVE PRODUCTS

5.1 B2-400

B2-400 is a clear gelatin two-piece capsule, size 00, filled with yellow-orange powder equaling 400 mg of Riboflavin (Vitamin B2). The near-infrared spectra of the powder matches the reference standard for riboflavin. The only inactive ingredient is the gelatin in the capsule which is kosher and halal certified. It will be manufactured by Biotech Pharmacal, Inc., Fayetteville, AR. The capsule is to be swallowed whole with food. Product testing shows it meets USP specifications for weight, heavy metals and Prop 65 specifications for heavy metals.

5.2 Placebo

Placebo will consist of a clear gelatin two-piece capsule, size 2, filled with white powder. There will be no active ingredients. Inactive ingredients include the gelatin capsule, which is kosher and halal certified, as well as microcrystalline cellulose powder. It will be manufactured by Biotech Pharmacal, Inc., Fayetteville, AR. The capsule is to be swallowed whole with food. Product testing shows it meets USP specifications for weight, heavy metals and Prop 65 specifications for heavy metals.

5.3 Investigative Product Receipt, Labeling and Storage

All study medications (B2-400 and placebo) will be received, stored, and dispensed by the University of Michigan Health System Research Pharmacy (UH B2D301). Block randomization will be used, as outlined in the statistics section below, and shared with the UMHS Research Pharmacy for proper dispensing of investigational products.

5.4 Source

Study subjects will be recruited from the University of Michigan Department of Dermatology outpatient clinics, and/or local announcement.

5.5 Characteristics of Study Group

Subjects will include up to 50 male or female subjects, 18 years of age or older, of any racial or ethnic background, and in good general health with chronic plaque psoriasis.

5.5.1 Inclusion Criteria

Subjects must meet all of the following criteria for inclusion in the study:

1. 18 years of age or older

2. Good general health

3. Willingness and ability to follow the protocol

4. Signed Informed Consent Form, written and witnessed.

5. Stable moderate to severe chronic plaque psoriasis involving 5% or greater total body surface area (TBSA).

6. If subject is a woman of childbearing potential, she must have a negative pregnancy test at screening and agree to use a medically acceptable form of contraception during the screening and throughout the study.

5.5.2 Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

1. Started using a topical steroid stronger than moderate strength, vitamin A or D analog preparations, or anthralin within 14 days of study drug initiation.

2. Initiated a systemic medications, including biologic medication, or phototherapy within 180 days of study drug initiation.

3. Prior or concurrent use of cyclophosphamide.

4. Currently using sulfasalazine therapy.

5. Known hypersensitivity to riboflavin.

6. Enrolled in any other investigational device or investigational drug trial(s) or receipt of any other investigational agent(s) within 28 days of baseline visit.

7. Presence of severe comorbidities such as, diabetes mellitus requiring insulin; CHF of any severity or myocardial infarction or cerebrovascular accident or transient ischemic attack within 3 months of screening visit; unstable angina pectoris, uncontrolled hypertension [sitting systolic BP <80 mm Hg or > 160 or diastolic BP > 100 mm Hg], oxygen-dependent severe pulmonary disease, history of cancer within 5 years [other than resected cutaneous basal or squamous cell carcinoma of the skin or in situ cervical cancer].

8. Any of the following hematologic abnormalities, confirmed by repeat test at least 1 week apart:

    - White blood count <3,000/μL or >14,000/μL

    - Lymphocyte count <1,000/μL

- Neutrophil count <1,5000/μL
- Platelet count <150,000/μL
- Hemoglobin<10 g/dL

9. Liver function test (aspartate aminotransferase [AST], alanine aminotransferase [ALT] or alkaline phosphatase [AlkP]) results that are greater than or equal to 2 times the upper limit of normal (ULN).

10. Serum creatinine ≥ to 2x the ULN.

11. Known HIV-positive status or known history of any other immune-suppressing disease.

12. Any current or past history of psychiatric disease that would interfere with ability to comply with study protocol or give informed consent.

13. Had grade 3 or 4 adverse events or infections within 28 days before screening, or between screening visit and drug initiation.

14. Evidence of any skin conditions other than psoriasis that would interfere with the evaluations of the effect of study medication on psoriasis.

15. Presence of any condition or circumstances judged by the patient's physician, the investigator, or medically qualified study staff to render this clinical trial detrimental or otherwise unsuitable for the patient's participation.

16. A history of non-compliance with other therapies.

17. Females who are pregnant, lactating, planning on pregnancy during the study period, or unwilling to use FDA-approved method of birth control.

18. A history of keloids or excessive scar formation or of healing poorly

19. A history of allergic reaction to local anesthetics, including lidocaine and epinephrine

6 STUDY PROCEDURES

6.1 Screening

The following are to be performed within 2 weeks prior to admission/Day 0:

1. Obtain written, witnessed informed consent

2. Review inclusion/exclusion criteria

3. Obtain complete medical history, history of previous psoriasis therapies, concomitant medications, and physical examination

4. For females of childbearing potential, obtain a negative urine pregnancy test.

5. Obtain 9 mL of blood to measure a complete blood count (CBC) and comprehensive metabolic panel (CMP).

6.2 Admission/Day 0

1. Measure vital signs.

2. Review medical history, adverse events and concomitant medications.

3. Skin Exam: Complete PASI, PGA, DLQI, and pruritus assessment using visual analog scale (VAS).

4. Photographs will be taken of significant lesions.

5. Randomize patient

6. For females of childbearing potential, obtain a negative urine pregnancy test.

7. 20 mL of blood will be drawn for measuring plasma levels of riboflavin and FAD.

8. Two psoriatic normal (PN) and two psoriatic plaque (PP) skin samples will be obtained (four total at this visit). These will be performed under local anesthesia (1% lidocaine with epinephrine) using a 6 mm skin punch to obtain skin through to subcutaneous fat. Closures will be made with 4-0 prolene sutures that should be removed in two weeks. Verbal wound care instructions will be provided.

9. Dispense medication.

6.3 Return Visits - Weeks 2, 6, 12, 16, 18, 22 and 28

1. Measure vital signs.

2. Review medical history, adverse events and concomitant medications.

3. Skin Exam: Complete PASI, PGA, DLQI, and pruritus assessment using visual analog scale (VAS).

4. For females of childbearing potential, obtain a negative urine pregnancy test.

5. Photographs will be taken of significant lesions on weeks 0, 12, 16, and 28.

6. One PP and one PN 6 mm punch biopsy will be performed at week 12. These will be performed as described above. This will be a total of 6 biopsies throughout the study.

7. 20 mL of blood will be drawn for measuring plasma levels of riboflavin and FAD on weeks 2, 12, 18 and 28.

8. 9 mL of blood will be drawn for measuring CBC, CMP on weeks 12 and 28.

9. At week 12 all residual medication will be collected and counted in preparation for patients to cross-over. There will be a four week wash-out period between weeks 12 and 16. At week 16 new medication will be provided and the data from this visit will be used as our new baseline for the second part of the study.

10. At week 28, all residual medication will be collected and counted.

6.4 Closeout Telephone Call at Week 32

1. Review medical history, adverse events, and concomitant medications.

2. Offer patient an in-office visit for any adverse events identified.

Table 1. Time and Events Table

	Screening	Week 0	Week 2	Week 6	Week12	Week 16	Week 18	Week 22	Week 28	Week 32 (phone)
Obtain informed Consent	X									
Randomization		X								
Medical and Psoriatic Treatment History	X	X	X	X	X	X	X	X	X	X
Physical Exam	X									
Con Meds/AE	X	X	X	X	X	X	X	X	X	X
Vital Signs		X	X	X	X	X	X	X	X	
PASI, PGA		X	X	X	X	X	X	X	X	
DLQI/ Pruritus VAS		X	X	X	X	X	X	X	X	
Urine Pregnancy Test for WOCBP	X	X	X	X	X	X	X	X	X	
Blood Draw (CBC/CMP)	X				X				X	
Blood Draw (FAD and Riboflavin)		X	X		X		X		X	
Biopsies		X			X					
Photographs		X			X	X			X	
Collect Residual Medication					X				X	
Dispense New Medication		X				X				

6.5 Premature Withdrawal from Study

Any subject who experiences adverse effects associated with study participation may be withdrawn from the study. Participation in the study may be discontinued for any of the following reasons:

1. Adverse events
2. Concurrent illness
3. Pain or discomfort during the study
4. Administrative reasons
5. Subject's decision to withdraw consent
6. Protocol violation.

Complete information on all adverse events will be recorded on an Adverse Event Report form (see Appendix E – Adverse Events LOG for a possible example). The Sponsor-Investigator will review all Adverse Events. The investigator will report adverse events that meet the standard IRBMED reporting guidelines (regarding relatedness and expectedness) to the University of Michigan Institutional Review Board and to the FDA as outlined in 21 CFR 312.32.

7 LABORATORY ASSESSMENTS

Biopsies will be processed for metabolomic profiling and will be taken from psoriatic normal (PN) as well as psoriatic plaque (PP) skin. Six 6 mm punch biopsies of the skin will be performed on each subject throughout the study. Two PN and two PP biopsies will be performed on week 0. Then one PN and one PP biopsy will be performed at week 12. For each subject, we will attempt to obtain all biopsies from the same plaque and the same area of normal skin. These biopsies will be divided in half and used for RNA profiling and histology.

Histological assessment will be performed for all patients using H&E, proliferation markers (Ki67), keratin 16, human beta defensin 2 (hBD2). Samples will be processed in batches of 10 patients at a time to limit batch-to-batch variation. To determine tissue responses, we will run a total of 20 patients for metabolomic and RNA-seq profiling.

All subjects will have a CBC, CMP drawn on screening and then at weeks 12, and 28. All patients in the study will have plasma measurements of riboflavin and FAD at weeks 0, 2, 12, 18, and 28. This will be a total of approximately 127 mL of whole blood per subject.

8 RISK AND RISK MITIGATION

The risks to subjects in this study are minimal, as riboflavin is a common over-the-counter supplement and the dose in this study has been well tolerated in previous studies (see Background Information). Side effects of diarrhea and polyuria have been reported, but these resolved promptly with discontinuation of riboflavin. There have been no reported deaths. Riboflavin toxicity is unlikely and also reversed promptly by discontinuation of the vitamin.

At study visits and the close-out telephone call, all subjects will be screened for adverse events. Any reported events will be recorded on a standardized form, similar to the example included in Appendix E – Adverse Events LOG. Basic labs will be drawn throughout the study, CBC and CMP, to monitor for potential toxicity to subjects' bone marrow, liver and kidneys. Pregnancy tests will be administered at each office visit to women of childbearing potential. As this dose of riboflavin has not been studied in pregnant women, any woman who becomes pregnant during the study will be discontinued.

Serious adverse events will be reported according to the UM IRB protocol in an expedited manner. These events include any untoward medical occurrence that results in: death, life threatening illness, hospitalization, persistent disability/incapacity, pregnancy, congenital anomaly/birth defect, an important medical event as deemed by the study investigators. Study investigators and staff will work together in this reporting.

9 DRUG ACCOUNTABILITY

Study administrators, Ms. Katherine Keeley and Jennifer Bell, will communicate with UMHS Pharmacy and coordinate the delivery of investigational medications. All investigational medications will be stored and dispensed to study administrators by the UMHS Research Pharmacy (UH B2D301), per protocol. These administrators will then hand subjects the investigational medication. At weeks 12 and 28, the study administrators will receive any excess investigational medication and record the number of returned capsules in the subjects file.

10 MONITORING PLAN

A risk-based approach to monitoring will be used for this study. The study has been assigned a risk level of "minor increase over minimal risk" with the University of Michigan Institutional Review Board (IRBMED). The study drug being used has a Generally Recognized as Safe (GRAS) designation from FDA and the Select Committee on GRAS (SCOGS) concluded that there is no hazard to the public when it is used at levels currently recommended by the FDA. This is a non-complex study that involves otherwise healthy subjects who are to be seen in an established and experienced research environment, with no electronic data capture using relatively safe study drug. For these reasons, the following monitoring plan will be implemented.

An onsite, independent, trained and experienced internal monitor will be assigned to monitor the progress of the study. The monitor will use existing standard departmental standards and guidelines in conducting the study review. The frequency of the review will be dependent on study activity, but will occur at least yearly. The first review will take place no more than 2 months from the enrollment of the first subject.

Processes/documentation to be reviewed by the monitor include:

- Communication between site staff IRBMED and subjects
- Verification of informed consent
- Adherence to protocol eligibility criteria
- Adherence to current documented protocol procedures
- Source documentation accuracy and completeness
- Procedures for documenting appropriate accountability and administration of the study drug
- Review adverse event reporting

Monitor will provide written results of the review including enrollment status, a description of any noncompliance or data irregularities, and any required corrective actions for significant issues found. Monitor will also confirm corrective actions were implemented and that reportable occurrences were reported to IRBMED. These reports will be submitted to IRBMED at the scheduled continuation review.

11 STATISTICAL METHODS

A block randomization schedule will be created and all subjects randomly assigned to a sequence of treatment and dispensed study product. Assuming a large effect size and a conservative amount of correlation between the measurements, a sample size of 22 subjects in each sequence yields a statistical power of 80%.

All clinical and laboratory assessments will be descriptively summarized at each visit (weeks 0, 2, 12, 16, 18, and 28) for the modified intent-to-treat population. Continuous variables will be summarized with standard descriptive statistics including mean, standard deviation and range. Categorical variables will be summarized by frequency and percentage (N, %).

Differences within each sequence of treatment from baseline to endpoint will be assessed using parametric general linear models such as the paired t-test. The two sequences will also be compared with respect to dichotomized improvement from baseline to the 12-week visit for key clinical endpoints using the McNemar test. Assuming no carryover effects due to the four-week washout period, all data will be pooled and used to estimate the treatment effect. An analysis testing the assumption of equal carryover effects will be performed. Wilcoxon signed rank test will be used to compare ordinal or nominal assessments. Parametric t-tests will be used to determine if continuous laboratory assessments are significantly different between the treatment groups.

An overall alpha-level of 0.05 will be used to determine statistical significance and all statistical tests will be two-sided. All data will be analyzed using SAS (SAS Institute, Inc., Version 9.3) software.

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13 Appendix A – Psoriasis Area And Severity Index (PASI)

Psoriasis Area and Severity Index (PASI)

SUBJECT ID: _____

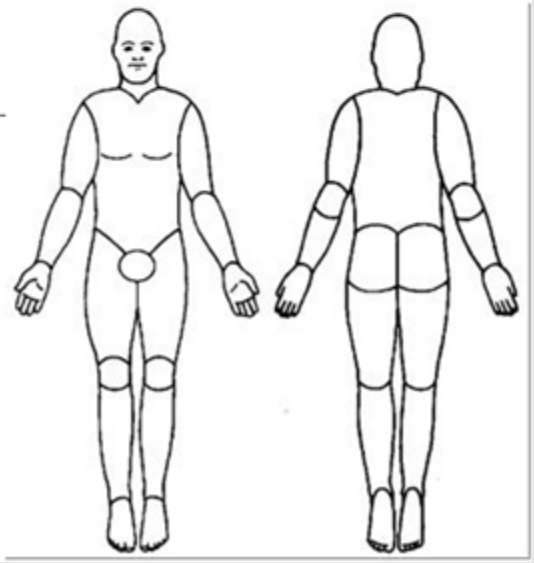
ASSESSMENT DATE: _____ **ASSESSOR INITIALS:** _____

Psoriasis Area and Severity Index (PASI): a quantitative rating scale for measuring the severity of psoriatic lesions based on area coverage and plaque appearance. Please complete all sections of the table and shade in the affected areas on the body diagrams below.

Plaque characteristic	Rating score	Body region (and weighting factor)			
		Head	Upper Limbs	Trunk	Lower Limbs
Erythema	0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very severe				
Thickness					
Scaling					
Add together each of the 3 scores for each of the body regions to give 4 separate sub totals.					
Sub Totals		A1=	A2=	A3=	A4=
Multiply each sub total by amount of body surface area represented by that region i.e. A1 x 0.1 for head, A2 x 0.2 for upper limbs, A3 x 0.3 for trunk, A4 x 0.4 for lower limbs to give a value B1, B2, B3 and B4 for each body region respectively					
		A1 x 0.1 = B1	A2 x 0.2 = B2	A3 x 0.3 = B3	A4 x 0.4 = B4
		B1=	B2=	B3=	B4=
Degree of involvement as % for each body region affected; (score each region with score between 0–6)	0 = None 1 = 1–9% 2 = 10–29% 3 = 30–49% 4 = 50–69% 5 = 70–89% 6 = 90–100%				
For each body region multiply sub total B1, B2, B3 and B4 by the score (0–6) of the % of body region involved to give 4 subtotals C1, C2, C3 and C4					
		B1 x score = C1	B2 x score = C2	B3 x score = C3	B4 x score = C4
		C1=	C2=	C3=	C4=
The patient's PASI score is the sum of C1+C2+C3+C4				PASI=	

Percent total body surface area (BSA) with psoriasis _____

Please shade in the affected areas:



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14 Appendix B - Static Physicians Global Assessment (sPGA)

Static Physicians Global Assessment (sPGA)

The sPGA is used to determine a subject's psoriasis lesions overall at a given time point. The sPGA score should be selected using the descriptors below that best describe the overall appearance of the lesions. It is not necessary that all three criteria be fulfilled. In some subjects either scaling or erythema will dominate the clinical presentation. In those cases, the sPGA score should be based on a combination of plaque elevation and the dominant feature (either erythema or scale). Since plaque elevation is the most robust finding, it should be the dominant feature influencing the sPGA rating for those indeterminate cases.

Score	Category	Category Description
0	Clear	Plaque elevation = 0 (no elevation over normal skin) Scaling = 0 (no scale) Erythema = 0 (residual post-inflammatory hyperpigmentation or hypopigmentation may be present)
1	Minimal	Plaque elevation = (possible but difficult to ascertain whether there is a slight elevation above normal skin) Scaling = (surface dryness with some white coloration) Erythema = up to moderate (up to definite red coloration)
2	Mild	Plaque elevation = slight (slight but definite elevation typically edges are indistinct or sloped) Scaling = fine (fine scale partially or mostly covering lesions) Erythema = up to moderate (up to definite red coloration)
3	Moderate	Plaque elevation = moderate (moderate elevation with rough or sloped edges) Scaling = coarser (coarse scale covering most of all of the lesions) Erythema = moderate (definite red coloration)
4	Severe	Plaque elevation = marked (marked elevation typically with hard or sharp edges) Scaling = coarse (coarse, non-tenacious scale predominates covering most or all of the lesions) Erythema = severe (very bright red coloration)
5	Very Severe	Plaque elevation = very marked (very marked elevation typically with hard sharp edges) Scaling = very coarse (coarse, thick tenacious scale covering most of all of the lesions; rough surface) Erythema = very severe (extreme red coloration; dusky to deep red coloration)

Physician's sPGA: _____
Evaluator's Initials:_____

15 Appendix C - Dermatology Life Quality Index

DERMATOLOGY LIFE QUALITY INDEX
DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑□one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	□ □ □ □
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	□ □ □ □
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all Not relevant	□ □ □ □ □
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all Not relevant	□ □ □ □ □
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all Not relevant	□ □ □ □ □
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all Not relevant	□ □ □ □ □
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No Not relevant	□ □ □
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	□ □ □

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all Not relevant	□ □ □ □ □
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all Not relevant	□ □ □ □ □
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all Not relevant	□ □ □ □ □

Please check you have answered EVERY question. Thank you.

16 Appendix D - Pruritus Assessment

Pruritus Assessment
Please rate your itch over the last 24 hours from 1-10 (10 being the worst)?

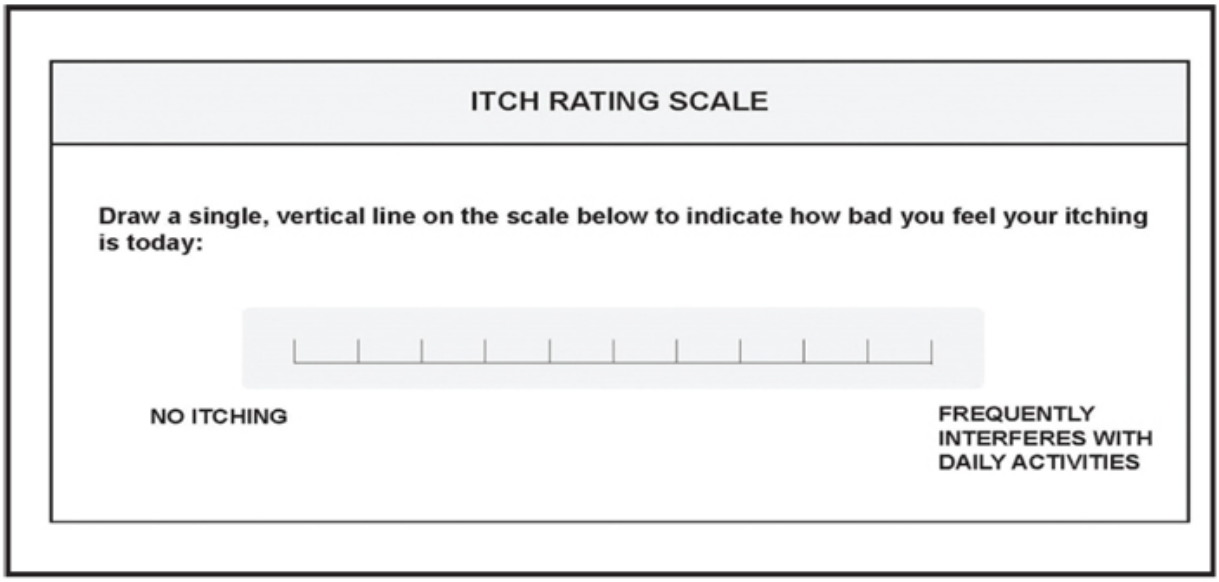

Figure 1. Visual analog scale

17 APPENDIX E – ADVERSE EVENTS LOG

Did the subject have any pre-existing conditions or experience any AEs while in the study?
YES ***NO***

Event Term	Start Date and Time	End Date	Severity	Outcome	Possibly related to study drug?	Possibly related to study procedure?	Serious?

SEVERITY: MILD, MODERATE, SEVERE **IF SEVERITY CHANGES, INDICATE DATE OF CHANGE AND NEW SEVERITY**: MILD, MODERATE, SEVERE, MORE SEVRE THAN BASELINE

OUTCOME: RESOLVED, RESOLVING, NOT RESOLVED, RECOVERED WITH SEQUELAE, FATAL, DISABILITY/INCAPACITY, WORSENED, UNKNOWN

IF SERIOUS, INDICATE ALL THAT APPLY: DEATH, LIFE THREATENING, DISABILITY, HOSPITALIZATION, CONGENITAL ANOMALY, OTHER, REQUIRES INTERVENTION

18 APPENDIX F - CONCOMMITANT MEDICATIONS LOG

Did the subject take any concomitant medications while in the study? ***YES*** ***NO***

Treatment Name	Start Date	End Date	Dose	Dose Unit	Treatment Frequency	Route	Indication*

***specify if primary study condition, prophylaxis or non therapeutic, pre-existing condition, or adverse event**