Protocol with Statistical Analysis Plan Cover Page:

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Abbreviated Title: NR in psoriasis

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Title: Pilot Study to Evaluate the Effect of Nicotinamide Riboside on Immune Activation in Psoriasis

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form

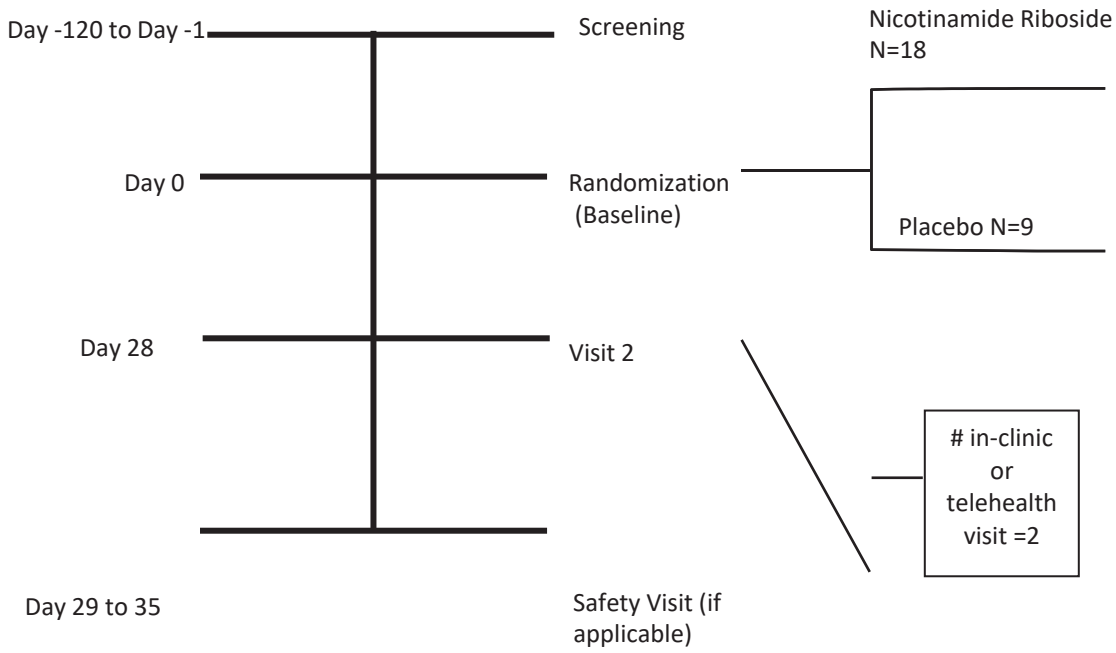
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Pilot Study to Evaluate the Effect of Nicotinamide Riboside on Immune Activation in Psoriasis
Study Description:	Psoriasis is a Th17 linked inflammatory disease and we find that the vitaminB3 analogue nicotinamide riboside (NR) blunts Th1 and Th17 activation in ex-vivo naïve and differentiated T cells from control and psoriasis subjects. These findings supported the proposal of the following hypothesis. Supplementation with NR will blunt systemic immune activation in mild/moderate psoriasis.
Objectives:	1) Evaluate the effect of NR on Th17 biology 2) Explore the effect of NR on neutrophils, specifically low-density granulocytes 3) Evaluate whether NR modulates keratinocyte activation in skin lesions in psoriatic subjects 4) Evaluate the effect of NR on HDL regulated reverse cholesterol transport and lipid composition
Endpoints:	The primary outcome will be the change in the T_H17 cell cytokine IL-17 secretion in response to T-cell differentiation comparing the baseline versus NR or placebo. The comparisons will be performed using paired two-tailed Student t-tests. Significance will be tested at the 0.05 alpha level in this pilot study. Exploratory outcomes are: 1) Evaluate the effect of NR on the T cell transcriptome 2) Explore the effect of NR on low-density granulocytes and neutrophils
Study Population:	Up to 40 male and female subjects of all races between the ages of 18-80 years with mild-moderate psoriasis who live locally will be screened.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	Enrollment and study visits will take place at the NIH Clinical Center or via telehealth visits . Psoriatic Subjects

Description of Study Intervention:	Nicotinamide Riboside Chloride 500mg or placebo twice daily by mouth for 28 days.
Study Duration:	3 years
Participant Duration:	5-23 weeks

1.2 SCHEMA


Day -120 to Day -1
Screening
Nicotinamide Riboside
N=18
Day 0
Randomization
(Baseline)
Placebo N=9
Day 28
Visit 2
in-clinic
or
telehealth
visit =2
Day 29 to 35
Safety Visit (if
applicable)

1.3 SCHEDULE OF ACTIVITIES (SOA)

EVALUATION AND ASSESSMENTS	Screening (A)	Baseline Visit*	28 day Visit *	Safety visit (if applicable)
PROTOCOL TIMEPOINT VISITS		1	2	3
		D0	D28	
Window +/- days	-120Days		+/- 7 D	
Assessments & Consents				
Review Inclusion/Exclusion Criteria	x			
Medical History	x			
Physical Examination	X[3]	X[3]	X[3]	X[3]
Medication Review	x	x	x	
Vital Signs		X[3]	X[3]	X[3]
Consent to Study	x	x		
Adverse Event Review			x	x
CHEMISTRY LABS				
Female, Pregnancy Test (blood or urine)	x[1]	x[1]	x[1]	
Acute Care Panel	x	x	x	x
Mineral Panel		x	x	x
Hepatic Panel	x	x	x	x
hs-CRP		x	x	x
Uric Acid	x			
Fasting Lipid Panel		x	x	
HEMATOLOGY LABS				
CBC with differential	x	x	x	x
Research Samples				
PBMC's		x	x	
Serum		x	x	
Procedures				
Skin Punch Biopsy (lesion and non-lesion)		X[3]	X[3]	
PASI (Psoriasis Area and Severity Index)	x			
Study Medication				
Dispense study pills		x		
Compliance (pill count)			x[2]	
Return of study pills			x	

A. Labs and assessments may be used for baseline visit if performed within 14 days

B. Unscheduled safety visit for those patients with clinically significant ongoing adverse events from month 1 visit or reported to site within 7 days from last dose of study drug. All procedures or testing noted above are optional.

x[1] = Pregnancy testing for women with childbearing potential
x[3] = Optional

x[2] = compliance to be greater than or equal to 75%
*Study visits are defined by the period of time necessary to complete events described in the protocol and may span several days.

All study visits may be performed in person at the NIH CC or virtually using NIH approved TeleMedicine software and approved NIH TeleMedicine guidance. In the event the subject is not able to come to the NIH CC the consent may be obtained by phone, vital signs are optional and reported based on subject's own measurements (if possible), physical exam is optional and none of these changes will be considered a protocol deviation. If there are remaining tablets, they will be returned to the research team at first possible opportunity following NIH pharmacy direction.

2 INTRODUCTION

2.1 STUDY RATIONALE

Over the past two decades, inflammation has been identified as an important pathogenic process in cardiometabolic diseases (CMD) such as atherosclerotic cardiovascular disease (CVD), dyslipidemia, insulin resistance, diabetes and obesity. Over the last eight years, the Mehta laboratory within the NHLBI DIR has studied psoriasis, a common, chronic inflammatory T-cell skin disease associated with increased CVD and CMD as a model to understand the effect of chronic inflammation on these disease states. At the same time, the degree of obesity has been linked to the severity of psoriasis and caloric restriction ameliorates dermatologic manifestations of this disease. The Sack laboratory is studying the effects of caloric restriction on immune activation and is demonstrating the caloric-restriction mimetic vitamin B3 analogue nicotinamide riboside (NR) blunts both adaptive and innate immunity. Furthermore, the in-vitro administration of NR to $CD4^+$ T cells extracted from psoriatic subjects blunts IL-17 production. Given this, these two laboratories will collaborate in a pilot study to evaluate whether the administration of a nutritional supplement NR has anti-inflammatory effects in a small cohort of subjects that have untreated mild to moderate psoriasis.

2.2 BACKGROUND

Psoriasis is a chronic inflammatory skin disease that affects 2–3% of the US population. In addition to its skin and joint manifestations, psoriasis predisposes to premature cardiovascular co- morbidities in part through immune activation and systemic inflammation-induced atherosclerosis.[1, 2] The skin-initiated immune- activation through non-professional immune cells including keratinocytes and fibroblasts, initiates and amplifies innate and adaptive immune activity of monocytes/macrophages, neutrophils and their subsets (low-density granulocytes), and effector T-cells (predominantly Th1 and Th17 subsets) which concurrently exacerbate local disease and initiate systemic sterile inflammation. The centrality of immune activation in psoriasis is reinforced by the therapeutic efficacy of anti-TNFα and anti-IL-17 therapy.[3-5]

The contribution of caloric-load to psoriasis has been long debated, however, epidemiology and meta-analysis data support that the incidence of obesity is higher in psoriasis and that the greater the severity of psoriasis, the higher the incidence of obesity.[6-8] The role of caloric excess in the pathophysiology of psoriasis is further strengthened by the effects of limiting calories on disease activity.[9-11] Taken together, these data support that nutrient levels may play a role in the pathophysiology of psoriasis and at the same time employing strategies to mimic caloric restriction/fasting may contribute to disease-amelioration.

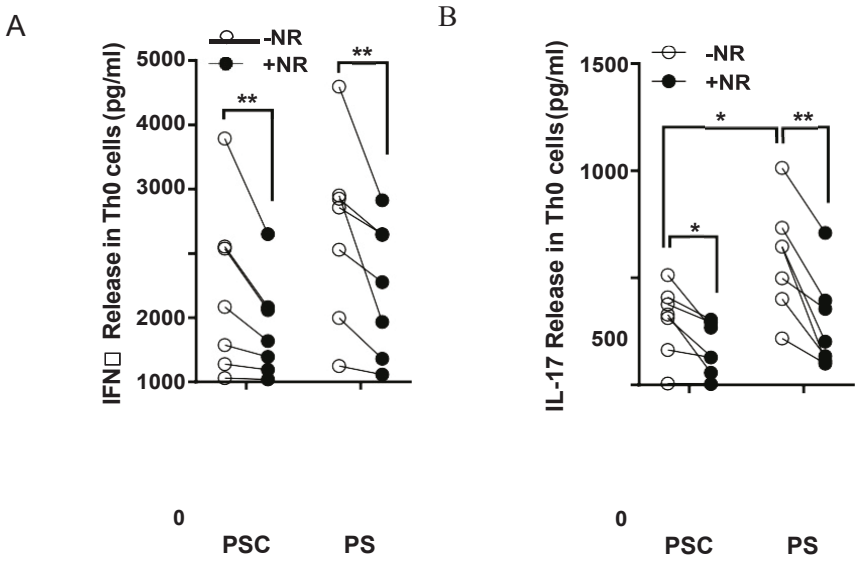
The Sack laboratory employs fasting as a model system to investigate immune cell function and have identified biological pathways that explain how fasting blunts immune activation in monocytes/macrophages and $CD4^+$ T cells in both healthy subjects and in those with a mild inflammatory disease (steroid-naïve asthma subjects). More recently we have begun to explore the role of a caloric restriction/fasting *mimetic*, nicotinamide riboside (NR – a vitamin B_3 analogue and precursor for NAD^+ biosynthesis) on immune modulation. Our initial clinic study using 1000 mg of NR daily blunted immune pathways important in CVD both in monocytes and $CD4^+$ T cells, however, we did not investigate the effects of NR on neutrophils.

Given that these cell types contribute to the pathophysiology of psoriasis and that disease activity may be ameliorated by dietary restriction, we reasoned that NR may blunt psoriasis-linked immune activation pathways. To explore this, a collaboration was established with the Mehta laboratory and the *in-vitro* effects of NR were tested on $CD4^+$ T cells extracted from biologic treatment-naïve psoriatic subjects. NR was found to blunt the secretion of IFNγ and IL-17, predominantly Th1 and Th17 cytokines respectively. Because these cytokines are instrumental in the progression of the dermatologic, systemic and vascular consequences in psoriasis, we propose a pilot interventional study to explore the immunological consequences of NR supplementation in biologic naïve, mild to moderate psoriatic subjects.

Preliminary Data:

To study the effect of NR on T cell function, blood was drawn from psoriatic subjects enrolled on protocol 13-H-0065 and from matched normal control subjects enrolled on protocol 16-H-0126. Psoriatic subjects were biological anti-immune therapy naïve. Primary peripheral bloodmononuclear cells (PBMCs) were isolated by density centrifugation. $CD4^+$ T cells were then negatively selected from PBMCs and cell purity was confirmed at > 95%.

$CD4^+$ T cells were activated in culture on plates coated with αCD3 and αCD28 antibodies for 3 days in the presence or absence of 0.5mM NR. Alternatively they were differentiated into two T cell subtypes by incubation with the specific polarization media (± NR) - Th1 (20 ng/ml IL-12 and 10 μg/ml αIL-4) and Th17 (20 ng/ml IL-6, 2 ng/ml TGF-β1, 10 ng/ml IL-1β, 10 ng/ml IL-23, 10 μg/ml αIL-4, and 10 μg/ml αIFNγ). Supernatants were collected, centrifuged to remove cells and debris, and stored at −80°C. The levels of cytokines, including IL-1β, IFNγ, IL-4, IL-5, IL-13, IL-17, IL-22, IL-9, IL-2, and MIP-1β were measured by ELISA (R&D Systems). Results were normalizedto cell number using the CyQuant cell proliferation and BCA protein assays.



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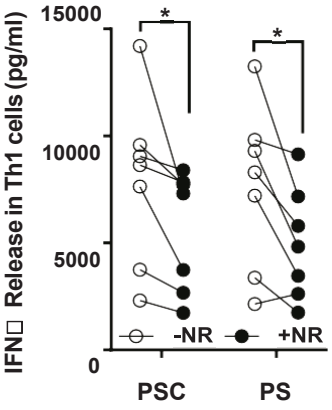
IFN□ Release in Th1 cells (pg/ml)
15000
10000
5000
0
*
*
-NR
+NR
PSC
PS

D

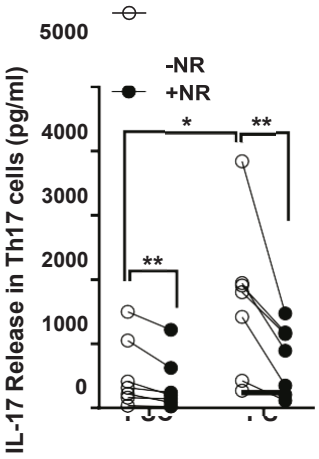
IL-17 Release in Th17 cells (pg/ml)
5000
4000
3000
2000
1000
0
-NR
+NR
*
**
**

Figure Legend: A, B. IFNγ and IL-17 release in activated CD4⁺T cells isolated from Psoriatic subjects (PS) and control subjects (PSC). CD4+T cells was activated with 0.5 mM NR and 10% autologous serum for 3 days by αCD3 and αCD28 (n=7). **C, D.** IFNγ and IL-17 release in differentiated CD4⁺T cells isolated from Psoriatic subjects (PS) and control subjects (PSC). CD4⁺T cells was differentiated with 0.5 mM NR and specific differentiation media with autologous serum for 3 days by αCD3 and αCD28 (n=6). Th1 differentiation supplement (Stemcell Technologies), Th17 differentiation supplement (R&D). PS age (y), 54.43±14.41 (range: 32-72); PS gender, 1 female and 6 males. Healthy volunteers (PSC) were paired with the psoriatic subjects for age (± 5 years) and sex. P value *<0.05 and **<0.01.

These data show that NR blunts Th1 and Th17 activation in naïve and differentiated T cells and that the psoriatic subjects exhibited elevated IL-17 responsiveness, which is a consistent signature of this disease. These findings supported the proposal of the following hypothesis.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 Known Potential Risks

Niagen has been sold as a dietary supplement in the United States since 2003. Labeling guidelines recommend consumers to limit their intake to 2 capsules/day (250 mg/day). This recommended level is the equivalent of 3.8 mg/kg body weight/day, which is 1000-fold less than the highest dose determined to be safe and well tolerated in rats, and there is no limit on the duration of ingestion.

There is extensive literature on the beneficial effects of NR in animal models,[12, 13] and multiple lines of non-clinical data suggest that it should be well tolerated in human subjects. In an acute toxicology study, rats that were given a single oral dose (5000 mg/kg) of NR did not show clinical signs of toxicity or mortality (unpublished results). The NR dose proposed for this study is within the doses tested in mice for up to 4 months and is 300-fold below the daily dose that was given in rats in a 14-day dose range finder study. There are also accumulating data on the pharmacokinetics and safety of orally administered NR in humans. Recently, a 2 x 6-week randomized, double-blind, cross-over study was performed to assess the tolerability of chronic NR supplementation and its efficacy for increasing NAD+ bioavailability. Here the oral administration of NR 500 mg twice daily (total 1000 mg daily, Niagen, ChromaDex, Inc.) was well tolerated, readily absorbed, and detectable in human plasma, white blood cells, and urine.[14] In a pharmacokinetic study of 8 healthy volunteers at the University of Washington, Seattle, the oral dose of NR dose was escalated from 250 mg daily to 1000 mg twice daily over a 9-day period with a resultant 100% increase in blood NAD+ content that highly correlated to NR levels.[15] No adverse events were associated with NR treatment in either of these two published human studies.

Niacin is a form of vitamin B3 and has been used to treat hypercholesterolemia and pellagra for many years. Niacin administration can lead to undesirable effects such as spontaneous flushing, but based on its pharmacology, NR would not be predicted to give this side effect.[16, 17] Indeed, the incidence of flushing side effect with NR treatment was not different compared with placebo in the double-blind study.[18] Nicotinamide, an expected metabolite of NR, is considered to be of low toxicity in food by several regulatory agencies including the United States Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA). Clinical trials of nicotinamide up to 3000 mg daily and 3 years in patients with or at risk of developing Type 1 diabetes have not reported significant adverse effects.[19, 20] In addition, doses of 25 and 42 mg/kg body weight per day had no effect on a variety of biochemical parameters including those assessing liver and kidney function.

In summary, careful analysis of the available information on NR does not reveal any potential serious toxicity that would preclude its use in psoriasis subjects. Given the safety and tolerability of NR in published human studies,[18, 21] and the favorable experience with NR in our NHLBI DIR protocol (16-H-0129, discussed in Background section), we propose to test the effect of NR in psoriasis patients at a dose 500 mg twice daily, a dose that is less than what is currently approved for use in other active clinical studies of the aforementioned groups.

The only tests and procedures done under this study are skin biopsies (optional), blood draws, and urine collection. The individual study procedure risks are listed below.

Skin biopsy: Two 4mm or smaller biopsies may be collected at visit 1 and visit 2 for a total of four skin biopsies. This procedure will be performed under local anesthesia. The entire procedure takes approximately 20 minutes. Discomfort at the biopsy site is usually mild and transient. This can be treated with minor analgesics. Normally, the risks include a reaction to the local anesthetic and the slight possibilities of local bleeding or infection. Scarring always occurs at the biopsy site.

Phlebotomy: Standard precautions for obtaining human blood samples will be taken. Transient discomfort and minor bruising may occur at the phlebotomy site. Vasovagal symptoms can occur during blood drawing. Blood samples will be obtained by venipuncture. The quantities of blood to be drawn for research purposes will be less than 550ml, which is consistent with the CC policy as provided in Medical Administrative Series (MAS) 95-9 (revised 5/29/12): for adults, no more than 10.5mL/kd or 550ml (whichever is smaller) will be drawn for research purposes over any 8 week period.

Known Potential Benefits

This supplement study has no prospect of direct benefit.

2.3.2 Assessment of Potential Risks and Benefits

The risks of the study supplement and the minor procedures included in this protocol are minimal and justified by the potential benefit of expanding our understanding of how nutrient levels may play a role in the pathophysiology of psoriasis and at the same time employing strategies to mimic caloric restriction/fasting may contribute to disease-amelioration. This supplement has been employed at the same or higher doses in numerous studies without any reported adverse effects.[14, 18, 21]

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Evaluate the effect of NR on Th17 biology	The primary outcome will be the change in the T_H17 cell cytokine IL-17 secretion in response to T-cell differentiation comparing the baseline to NR response.	NR blunts Th1 and Th17 activation in naïve and differentiated T cells and psoriatic subjects exhibit elevated IL-17 responsiveness, which is a consistent signature of this

		disease.
Exploratory		
		The primary driver of psoriasis does appear to be
OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Explore whether other inflammatory components linked to psoriasis are affected by NR.	Evaluate the effect of NR on the T cell transcriptome Explore the effect of NR on neutrophils, specifically low-density granulocytes	Th17, however, other immune signals and cell types are linked to psoriasis including, neutrophil activation, skin keratinocyte activation and the accumulation of HDL in monocytes/macrophages is proposed to trigger inflammatory pathways. We will explore the effect of NR on modulating these cell types and pathways as exploratory end points

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is a pilot, prospective, two-arm double-blind, placebo-controlled study where subjects immunological profile will be studied at baseline and following 4 weeks of supplementation with NR or placebo. The allocation of NR: placebo will be 2:1. All enrolled subjects will receive NR or placebo and following 4 weeks of supplement or placebo intake, research parameters will be compared to baseline to determine the effects of this intervention.

SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a pilot study and the number of subjects were chosen to allow us to have sufficient samples to use RNAseq analysis to explore the effects of NR on T cell biology if the primary outcome of the study is confirmed.

4.2 JUSTIFICATION FOR DOSE

Recently, a 2 x 6-week randomized, double-blind, cross-over study was performed to assess the tolerability of chronic NR supplementation and its efficacy for increasing NAD+ bioavailability by investigators at the University of Colorado, Boulder.[14] They demonstrated that the oral administration of NR 500 mg twice daily (total 1000 mg daily, Niagen, ChromaDex, Inc.) was well tolerated, readily absorbed, and detectable in human plasma, white blood cells, and urine.

5. STUDY POPULATION

ELIGIBILITY ASSESSMENT AND ENROLLMENT

All protocol eligibility criteria will be met before dispensing study medication to participants or conducting the biopsy for the baseline visit. Patients will sign the consent prior to any screening tests/procedures done as part of this protocol.

5.1 INCLUSION CRITERIA

Individuals must meet all inclusion criteria listed below in order to be eligible to participate in the study.

- Males and females between the ages of 18 and 80 with mild to moderate active psoriasis.
- Female subjects of child-bearing ability willing to commit to reliable contraception while participating in the study.
- Ability to provide informed consent
- Willingness and ability to participate in required study procedures

5.2 EXCLUSION CRITERIA

- Severe psoriasis by PASI (Psoriasis Area and Severity Index) score > 12
- Currently being treated with biologic immune modifying agents.
- Currently on treatment for allergies or other inflammatory diseases.
- Currently taking a multivitamin, Vitamin B or tryptophan supplementation and unwilling to stop within 2 weeks of baseline visit..
- Unwillingness/inability to provide informed consent
- ALT > x3 upper limit of normal, hepatic insufficiency or active liver disease
- Recent history of acute gout
- Chronic renal insufficiency with creatinine > 2.5mg/dl
- Pregnant (or attempting to become pregnant) women
- Current participation in another drug study
- History of intolerance to NR precursor compounds, including niacin or nicotinamide
- Study adherence concerns
- Individuals with diabetes type 1 and 2 who use insulin
- Women of child-bearing potential unwilling to use contraception or unwilling to practice abstinence
- Breastfeeding women unwilling to stop breastfeeding
- Immunization administered within 30 days of participation and no plans for immunization while participating in the study

5.3 INCLUSION OF VULNERABLE PARTICIPANTS

Rationale for the Exclusion of Children

Subjects under 18 years of age will not be considered for inclusion in this protocol because there is no direct benefit from participating in this study and the volumes of blood levels drawn exceed

minimal risk for children

Rationale for the exclusion of pregnant women
The subject must not be pregnant or actively seeking pregnancy in order to participate in this study. NR has not been determined to be safe in pregnancy or breastfeeding women. A recognized form of contraception must be used by subjects while enrolled. Contraception use will be determined during telephone screening and confirmed at the screening visit.

Rationale for the exclusion of cognitively impaired subjects
Subjects with cognitive impairment will not be considered for inclusion because there is no direct benefit from participating in this study.

5.4 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Refrain from making major changes in dietary intake or physical activity during the 6 weeks of active study participation.

5.5 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention. These subjects will sign consent and will receive a study id.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened at a later date at PI discretion. Individuals who do not meet criteria for participation based on an abnormal laboratory test result may be rescreened after one month.
Rescreened participants will be assigned a new participant id number from the initial screening.

5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects with mild to moderate psoriasis will be recruited from Dr. Mehta's psoriasis clinic. We will also recruit subjects through NIH using traditional recruitment methods such as referrals from other protocols, outside physician referral and self-referral.

With IRB approval the study may opt to use the following strategies for recruitment of patients:

- ClinicalTrials.gov
- Clinical Center Research Studies website
- National Heart, Lung and Blood Institute (NHLBI) patient recruitment website
- Twitter messages and chats with study investigators
- Social Media posts
- Use of CC Office of Patient Recruitment services including creation and distribution of study flyers and information through pre-existing recruitment avenues such as the NIH recruitment listserv.

We expect to screen up to 40 subjects with a goal of 27 subjects (18 NR + 9 placebo) completing the study.

5.6.1 Costs

There will be no anticipated costs that the subject will be responsible for.

5.6.2 Compensation

Subjects will be compensated for some of the procedures that are performed since they may not provide direct benefit to the subject. They will be compensated by check or direct deposit at the end of the study or at the time of study withdrawal for the procedures completed. Payment will typically be received within 2 months of the last study visit.

Procedures	**Convenience Units**	**Compensation per procedure**	**Frequency**	**Total Compensation**
Medical History	2.5	$25.00	1	$25.00
Screening Blood Draw (if needed)	1	$10	1	$10
Research Blood Draw	5	$50.00	2	100.00
Research skin biopsy	5	$50.00	4	$200.00
Drug administration, General	2	$20.00	28	$560.00
Maximum Compensation:				$895.00

Reimbursement for travel, food, and lodging will not be provided.

6 STUDY INTERVENTION

6.2 STUDY INTERVENTIONS(S) ADMINISTRATION

6.1.1 Study Intervention Description

The study will use the dietary supplement Nicotinamide Riboside or a placebo capsule. Niagen®is a commercially-available form of nicotinamide riboside (NR). The nucleoside NR is a single chemical moiety containing nicotinamide and ribose.[22] NR is a form of vitamin B3 present in trace amounts in foods like milk, yeast extract and beer. It is also postulated that NR is generated inthe gastrointestinal tract as part of dietary NAD+. Thus, humans are constantly exposed to NR from the diet, albeit at low levels. Considering the clinical investigation is designed to study the relationship between a dietary supplement's effect on structure or function in humans or to characterize the mechanism by which a dietary supplement acts to maintain such structure or function, this study would not need to be conducted under an IND. Under the Dietary Supplement Health and Education Act of 1994, a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic

purpose). Similarly, whether an IND is needed for a clinical investigation evaluating a dietary supplement is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required.

6.1.2 Dosing and Administration

N/A

6.1.3 Dose Escalation

N/A

6.1.4 Dose Limiting Toxicity

N/A

6.1.5 Dose Modifications

N/A

6.1.6 Drug Administration

Subjects will take two capsules by mouth (250mg NR capsules or placebo) twice daily for a total of 4 weeks (+/- up to 5 days if needed). Capsules must be taken whole and may be taken with or without food. Doses should be approximately 12 hours apart but there should be a minimum of 6 hours between doses. If a dose is missed and it is more than 6 hours before the next dose is due then the dose can be taken. If a dose is missed and it is less than 6 hours before the next dose is due then the missed capsules should be skipped.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 Acquisition and Accountability

Both the NR and placebo will be obtained from Chromadex. It will be stored and dispensed by the NIH CC Pharmacy. Unused product will be returned to the clinical center and destroyed.

6.2.2 Formulation, Appearance, Packaging, and Labeling

Common name: Nicotinamide Riboside Chloride
Product name: Niagen
Chemical name: 3-(Aminocarbonyl)-1-β-D-ribofuranosyl-pyridinium chloride (1:1)
Daily dose: 1000 mg x 4 wk,
Route of administration: oral
Dosing instructions: 500 mg (2 capsules) twice daily Supply:Supplements will be obtained from Chromadex.
Toxicology: None known

Drug Interactions: None known

The capsules will be put into individual bottles, labeled and dispensed by the NIH Clinical Center pharmacy. The label will include at a minimum the study ID and instructions for taking the supplement or placebo.

The placebo will be manufactured and supplied by Chromadex to match the active supplement.

6.2.3 Product Storage and Stability

NR and placebo will be stored in the pharmacy at room temperature in light restricted containers.

6.2.4 Preparation

N/A

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Dr. Myron Waclawiw (BioStatistical Co-Investigator on the study) will devise a randomization code . The code will be employed by the pharmacy to dispense the study pills. The study team will be blinded to the code until enrollment is complete and the assays performed for the primary end point.

6.4 STUDY INTERVENTION COMPLIANCE

Study capsule compliance will be assessed based on patient report and we will perform capsule count at Visit 2. If Visit 2 takes place remotely, the investigator will observe the research subject counting the remaining pills. Blood NAD^+ metabolic intermediate levels will be tested at visit 2 to confirm compliance.

6.5 CONCOMITANT THERAPY

Subjects should not take any biologic immune modifying agents, other multivitamins, vitamin B or tryptophan supplements for the duration of the study.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation Of Study Intervention

The supplement has a good safety record and we do not expect any significant adverse events. However, if a grade 3 or higher adverse event related to the supplement occurs, the study will be halted pending discussions with the NIH IRB and the NHLBI Clinical Director.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

1) Subject taking less than 75% of their capsules
2) Subject found to be pregnant or wishes to breastfeed during the study will automatically be withdrawn
3) If subject no longer wish to participate
4) Subject's non-compliance or per PI discretion for development of a condition that may independently affects immune activity.

Prior to removal from study, any subject who has started the study intervention should complete a safety visit. For subjects who complete the study, this would be included in Visit 2. If a subject requests withdrawal early for any reason, we will make every effort to have them complete an

unscheduled safety visit..

The reason for participant discontinuation or withdrawal from the study will be recorded in the source document. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced until the recruitment goals of 18 NR and 9 placebo subjects have completed the protocol. Participants who are withdrawn for reasons that are temporary, such an infectious disease or administration of an immunization, may be re-screened and if they meet eligibility then re-enrolled with a new study id.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit, specify time frame and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 attempts at contact) These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCREENING PROCEDURES

Subjects with mild to moderate psoriasis will be recruited from Dr. Mehta's psoriasis clinic at the NIH or from outside and self- referrals If a subject is recruited from a source outside the NIH then the screening and/or baseline visit #1 will be in person. The remainder of the visits may be via telehealth.

Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.

Once the research team has identified a potential subject for the study, the subject will be asked to come to the NIH or complete a Telehealth Screening Visit. The study team will consent the subject, allowing time for the subjects to ask questions and make a voluntary decision.

Once the subject signs the consent, the following tests will be done at the Screening Visit unless any of the tests have been performed under another NIH protocol 2 weeks prior to signing the consent (unless otherwise stated).

Screening Visit (May be combined with Visit 1):

- Basic Metabolic Panel
- Hepatic Panel + uric acid
- CBC + Differential
- Serum pregnancy test for women with childbearing potential (within the past 24 hours)
- History +/- physical exam (physical exam will not be performed at TeleHealth visit)

8.2 EFFICACY ASSESSMENTS

This study is designed to study the relationship between a dietary supplement's effect on structure or function in humans or to characterize the mechanism by which a dietary supplement acts to maintain such structure or function. It is not designed as an efficacy study. Therefore, visits will focus on safety assessments as well as the collection of research blood and skin biopsies (optional). These collections will be performed at the NIH CC phlebotomy department when feasible however collection at an outside laboratory, such as a commercial or hospital-based lab, may be arranged if needed.

8.2.1 Clinical Evaluations

Radiographic or other imaging assessments.

N/A

8.2.2 Biospecimen Evaluations

Biological specimen collection and laboratory evaluations. In addition to the clinical blood samples, subject will have research bloods drawn within the blood withdrawal volume limits established by the Clinical Center. RNAseq, Flow cytometry, metabolomics, HDL cholesterol uptake and cytokine profiling may be performed. Skin biopsy samples may be obtained for culture or isolation of distinct cell populations for subsequent biochemical, cell biological and molecular analyses and for immune-histochemistry. With the patient's consent, a biopsy each of lesional skin (where there is active psoriasis) and non-lesional sites (where there is no psoriasis) will be performed, and hemostasis will be achieved. The skin biopsy will be performed by a healthcare provider and will be used primarily for research purposes.

Test/assay	Volume blood (approx.)	Type of tube	Collection point (+/- 48hrs)	Location of specimen analysis
Immune-monitoring	80 mls for PBMC's and NAD+. 20mls for Neutrophils. 20mls for low density granulocytes (LDG's).	Green Tops for PBMC's and NAD+ Green Tops for Neutrophils Green Tops for LDG's	Baseline and 4 weeks.	10-CRC, Room 5-3216 Lab (Deliver to Dr. Sack's lab)
	5-10mls (for serum)	Red top		
HDL reverse transport	2mls	Purple top	Baseline and 4 weeks	Dr. Mehta lab

8.2.3 Correlative Studies for Research/Pharmacokinetic Studies

N/A

8.2.4 Samples for Genetic/Genomic Analysis

N/A

8.3 Safety and Other Assessments

Laboratory tests will be assessed at baseline and at 4 weeks. Adverse event review will occur at 4 weeks.

Counseling: Subjects should maintain a stable diet and not start any new diets or exercise programs for the duration of the study.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definition of Adverse Event

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.4.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.4.3 Classification of an Adverse Event

8.4.3.1 Severity of Event

This study will utilize the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) for toxicity and adverse event reporting. A copy of the CTCAE v5.0 can be downloaded from the https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs classified as Grade 2-5 will be recorded, verified, and followed until satisfactory resolution or stabilization. In the event of any treatment-related SAEs, enrollment will be suspended until discussed with the IRB and Clinical Director.

Grading and attribution of adverse events

Severity definitions found in the CTCAE v5.0 will be used for grading the severity (intensity) of AEs:

1) **Mild**: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2) **Moderate:** Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
3) **Severe:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4) **Life- threatening:** Life-threatening consequences; urgent intervention indicated.
5) **Death:** Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.4.3.2 Relationship to Study Intervention

- All Grade 2-5 adverse events (AEs) must have their relationship to study intervention assessed by the investigator or designee who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty

about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.4.3.3 Expectedness

The PI or designee will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or

frequency of the event is not consistent with the risk information previously described for the study intervention. We expect some vasovagal symptoms during blood draws (expected frequency 50%) and transient bruising at the site of blood draws (expected frequency 50%).

8.4.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Investigators will assess the occurrence of AEs and SAEs at all patient evaluation time points during the study. Grade 2 – 5 AEs/SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, clinically significant laboratory test, or other means will be recorded on the appropriate case report form. . Information to be collected on Grade 2-5 AE/SAE includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All Grade 2-5 AEs will be followed to adequate resolution or stabilization.

Abnormal laboratory values not associated with clinical symptoms (except for grade 2 elevated liver enzymes) will be evaluated but will not be considered an AE. The laboratory results will be monitored by healthcare professionals and documented if clinically significant by the MD or any AIs in the study.

Psoriasis is a chronic disease associated with flares and we will record this information in the medical record.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

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

8.4.5 Adverse Event Reporting

Grading and attribution of AE's captured in the database will be determined by the Principal Investigator or Associate Investigator's designated on the designation log.

8.4.6 Serious Adverse Event Reporting

The study investigator will immediately report to the NHLBI Clinical Director any serious adverse event, whether or not considered study intervention related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

Any SAE considered at least possibly related to the supplement will be reported to the DSMB within 14 days of the investigator being notified of the event.

8.4.7 Events of Special Interest

N/A

NIH Intramural IRB and NHLBI Clinical Director (CD) Reporting

Expedited Reporting

Events requiring expedited reporting will be submitted to the IRB per HRPP Policy 801 "Reporting Research Events".

Reports to the IRB at the time of Continuing Review (CR):

The PI or designee will refer to HRPP Policy 801 "Reporting Research Events" to determine IRB reporting requirements.

Reports to the CD:

The PI or designee will refer to NHLBI DIR guidelines to determine CD reporting requirements and timelines.

8.4.8 Reporting of Pregnancy

If pregnancy occurs during the course of this study a reportable event form will be submitted to the Clinical Director and the IRB.

Pregnancy itself is not regarded as an SAE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Any SAEs associated with pregnancy (i.e. congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE report form. Monitoring of the pregnancy through chart review (per HIPPA guidelines) will continue until conclusion of the pregnancy, and then subject will be taken off study.

8.5 UNANTICIPATED PROBLEMS

8.5.1 Definition of Unanticipated Problems (UP)

Please refer to Policy 801 for current Definitions.

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

8.5.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board

(IRB) as per Policy 801.

8.5.3 NIH Intramural IRB Reporting of IND Safety Reports

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESIS

Supplementation with NR will blunt systemic immune activation in mild/moderate psoriasis.

Primary Endpoint(s): The primary outcome will be the change in the T_H17 cell cytokine IL-17 secretion in response to T-cell differentiation comparing the baseline to NR response after 28 days.

Exploratory Endpoint(s):

- Evaluate the effect of NR on the T cell transcriptome
- Explore the effect of NR on low-density granulocytes and neutrophils

9.2 SAMPLE SIZE DETERMINATION

Sample size calculations for this pilot study were based on the two-sample t-test assuming equal variances with a two-sided alpha of 0.05 and a 2:1 (unequal) allocation of subjects NR: placebo. A previous in-vitro study (unpublished to data) yields data for IL-17 levels (pg/ml) for T-cells extracted from psoriatic subjects at baseline and after 72 hours of exposure to 0.5 mM nicotinamide riboside (NR). The observed mean change in IL-17 cytokine release was 329 pg/ml (from 600 to 271 pg/ml) with a standard deviation of 185.74 for the 72-hour changes. For the proposed in-vivo study, we assume a similar change in mean IL-17 (and standard deviation) for psoriatic subjects treated with NR for 4 weeks. For the control subjects receiving placebo, we assume a mean baseline to 4 weeks change in IL-17 of 0 and an equal standard deviation of 185.74 for the 4-week changes.

In the table below, we present power calculations for various scenarios. With 18 subjects on NR and 9 on placebo, the study will have 98% power to detect a difference of 329 pg/ml in the mean baseline to 4-week changes between the two study groups (scenario 1). Note that there will still be 82% power to detect a smaller mean difference of 229 pg/ml between the two study arms (a 100 pg/ml difference less than that achieved in the in-vitro study) should the control subjects exhibit up to a 100 pg/ml decrease in IL-17 due to a placebo effect (scenario 2). Furthermore, even with a loss to follow-up of 3 subjects (2 in the NR arm, 1 on placebo), the study will have 97% power to detect a mean change of 329 pg/ml (scenario 3), and a reduced power just under 80% for a strong placebo effect with a mean difference = 229 pg/ml (scenario 4). Therefore, we request approval to screen up to a total of 40 subjects to account for possible treatment non- compliance and/or study dropouts (18 NR + 9 placebo completing study) and to achieve the objectives of this pilot study.

Scenario	**1**	**2**	**3**	**4**
#Subjects treated with NR	18	18	16	16
# subjects on placebo	9	9	8	8
Difference in means	329	229	329	229
Power	98%	82%	97%	77%

9.3 POPULATIONS FOR ANALYSES

N/A

9.3.1 Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with study supplement or placebo.

9.3.2 Evaluable for objective response

N/A

9.4 STATISTICAL ANALYSES

9.4.1 General Approach

9.4.2 Analysis of the Primary Endpoints

The primary outcome will be the change in the T_H17 cell cytokine IL-17 secretion in response to T-cell differentiation comparing baseline levels versus their respective response to NR or placebo. The comparisons will be performed using paired two-tailed Student t-tests or if the data is not normally distributed, by the Wilcoxon test. Significance will be tested atthe 0.05 alpha level in this pilot study.

9.4.3 Analysis of the Secondary Endpoint(s)

N/A

9.4.4 Safety Analyses

N/A

9.4.5 Baseline Descriptive Statistics

N/A

10 REGULATORY AND OPERATIONAL CONSIDERATIONS

10.1 INFORMED CONSENT PROCESS

10.1.1 Consent/Assent Procedures and Documentation

Informed consent will be conducted following OHSRP Policy 301- Informed Consent.

An IRB-approved consent form will be provided to the participant electronically or by hard copy for review prior to consenting. The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved platforms). The investigational nature and objectives of this trial, the procedures, and their attendant risks and discomforts and potential benefits will be carefully explained to the participant in a private setting. The participant will be given as much time as they need to review the document and to consult with their family, friends, and personal health care providers. In addition, a study team member will be available to answer any questions.

A signed and dated informed consent document will be obtained by any investigator authorized to consent (See Key Study Personnel Page) prior to entry onto the study. Consent may be obtained with required signatures on the hard copy of the consent or on the electronic

document.

When a document that is in electronic format is used for obtaining consent, this study may use the iMed platform which is 21 CFR, Part 11 compliant, to obtain the required signatures.

During the consent process, participants and investigators may view the same approved consent document simultaneously when participant is being consented in person at the Clinical Center or both may view individual copies of the approved consent document on screens in their respective locations remotely. Signatures may be obtained either by both directly signing on the device that the consenting investigator is using (when in person) or through iMed Mobile Signature Capture (remotely) which allows texting or emailing a link to the participant. That link allows the participant to review the consent, then proceed to sign on the device they are using.

Whether hard copy or electronic, both the investigator and the participant will sign the document with a hand signature using a pen (if using hard copy), finger, stylus, or mouse (if electronic).

When done remotely, if the participant prefers to sign a hard copy, they may be instructed to sign and date the consent document during the discussion and mail, secure email or fax the signed document to the consenting investigator.

Whether in person or remotely, the privacy of the participant will be maintained.

Finally, the fully signed informed consent document will be stored in the electronic medical record, and the participant will receive a copy of the signed informed consent document.

The informed consent process will be documented on a progress note. The date the signed informed consent document was received from the subject and signed by the consenting investigator will be documented in the consent progress note.

10.1.2 Consent for minors when they reach the age of majority

N/A

10.1.3 Telephone consent

Informed consent may be obtained over the telephone or by telemedicine/videocall rather than in person. Informed consent will be obtained per HRPP Policy 301. Subjects will be contacted by telephone by the PI or AIs approved to obtain consent. The consent process obtained by the phone or videocall will be identical to a consent obtained in person. The investigational nature and research, objectives of the trial, procedures, risks and discomforts will be carefully explained to the subject. If the subject(s) choose(s) to participate, a signed informed consent will be obtained. The subject will sign and date the informed consent. The informed consent document may then be faxed, sent via NIH secure email, and will be mailedback to either the investigator or to an authorized team member. The PI or AI approved to obtain consent will then sign and date the received consent. The original consent will be sent to medical records. The informed consent process will then be documented in CRIS. At this point the subject will be considered enrolled in the study. The subject will receive a copy of the signed consent either by FAX, secure e-mail, mail or by hand, at his first visit to the CC for this study.

10.1.4 Participation of Subjects who are/become Decisionally Impaired

N/A

10.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

10.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the NIH for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored in a research database in conformity with NHLBI DIR policy. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the research staff will be secured and password protected.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to

participants.

10.3 FUTURE USE OF STORED SPECIMENS AND DATA

We may share specimens and data with other researchers for future use.

Following analyses of biospecimens for primary research purposes as described in the protocol, remaining samples suitable for future research will be stored in manner that conforms with DIR policy (such as BSI) or in a publicly accessible research biospecimen repository following IRB approval. Biospecimens may be destroyed only when permitted by the clinical director and approved by the IRB. Any future research use of biospecimens not defined in the research protocol will occur only after IRB review and approval, if the research holds the key that identifies research subjects, or determination from OHSRP (non-collaborative research).

10.4 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined.
The DSMB will provide its input to National Institutes of Health staff.

10.5 CLINICAL MONITORING

The monitoring of this study will be conducted by clinical research associates (CRAs)/monitors employed by an independent contract organization working under an agreement with NHLBI to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent form (ICF) and documentation of the ICF process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs;

3) to compare abstracted information with individual subjects' records and source documents (subject's charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections-OHRP) and applicable guidelines (ICH-GCP) are being followed. Monitoring will be conducted according to the OCD schedule. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (e.g., consent forms and pertinent hospital or clinical records readily available for inspection by the local IRB, the site monitors, and the NHLBI staff for confirmation of the study data.

10.6 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.7 DATA HANDLING AND RECORD KEEPING

10.8.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data and clinical laboratory data will be entered into CTDB, a 21 CFR Part 11-compliant data capture system. Clinical data will be entered directly from the source documents.

10.8.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2

years have elapsed since the formal discontinuation of clinical development of the study intervention, or as per the NIH Intramural Records Retention Schedule. No records will be destroyed without the written consent of the NHLBI Clinical Director.

10.8 PROTOCOL DEVIATIONS

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations to the NIH Institutional Review Board as per Policy 801.

NIH Definition of Protocol Deviation

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.

- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of subjects or others, or the scientific integrity or validity of the study.

10.9 PUBLICATION AND DATA SHARING POLICY

10.10.1 Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Study participants may be notified by mail or secure email when results are posted on Clinicaltrials.gov or when a manuscript is posted. Data from this study may be requested from other researchers 3 years after the completion of the primary endpoint by contacting Dr. Michael Sack at the NHLBI

10.10.2 Genomic Data Sharing Plan

N/A

10.10 COLLABORATIONS AND AGREEMENTS

10.11.1 Agreement Type

CRADA: A CRADA between NHLBI and Chromadex for the conduct of this study is being executed.

MTA: We will send coded PBMC for analysis of metabolic pathways to Kennedy Institute, Oxford University UK (Dr. Alexander Clarke). The collaborator will not have access to the code key. Upon receipt of the data analysis, NHLBI will link the analyzed data to identifiers. We will not send samples outside NIH without an executed material transfer agreement (MTA).

10.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NHLBI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

12 REFERENCES

1. Lerman JB, Joshi AA, Chaturvedi A, Aberra TM, Dey AK, Rodante JA, Salahuddin T, Chung JH, Rana A, Teague HL, Wu JJ, Playford MP, Lockshin BA, Chen MY, Sandfort V, Bluemke DA and Mehta NN. Coronary Plaque Characterization in Psoriasis Reveals High-Risk Features That Improve After Treatment in a Prospective Observational Study. *Circulation*. 2017;136:263-276.

2. Dey AK, Joshi AA, Chaturvedi A, Lerman JB, Aberra TM, Rodante JA, Teague HL, Harrington CL, Rivers JP, Chung JH, Kabbany MT, Natarajan B, Silverman JI, Ng Q, Sanda GE, Sorokin AV, Baumer Y, Gerson E, Prussick RB, Ehrlich A, Green LJ, Lockshin BN, Ahlman MA, Playford MP, Gelfand JM and Mehta NN. Association Between Skin and Aortic Vascular Inflammation in Patients With Psoriasis: A Case-Cohort Study Using Positron Emission Tomography/Computed Tomography. *JAMA Cardiol*. 2017;2:1013-1018.

3. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, Gottlieb AB and Etanercept Psoriasis Study G. Etanercept as monotherapy in patients with psoriasis. *The New England journal of medicine*. 2003;349:2014-22.

4. Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, Braun D and Banerjee S. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *The New England journal of medicine*. 2012;366:1190-9.

5. Mease PJ. Inhibition of interleukin-17, interleukin-23 and the TH17 cell pathway in the treatment of psoriatic arthritis and psoriasis. *Curr Opin Rheumatol*. 2015;27:127-33.

6. Sterry W, Strober BE, Menter A and International Psoriasis C. Obesity in psoriasis: the metabolic, clinical and therapeutic implications. Report of an interdisciplinary conference and review. *Br J Dermatol*. 2007;157:649-55.

7. Azfar RS and Gelfand JM. Psoriasis and metabolic disease: epidemiology and pathophysiology. *Curr Opin Rheumatol*. 2008;20:416-22.

8. Armstrong AW, Harskamp CT and Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. *Nutr Diabetes*. 2012;2:e54.

9. Ricketts JR, Rothe MJ and Grant-Kels JM. Nutrition and psoriasis. *Clin Dermatol*. 2010;28:615-26.

10. Di Minno M N, Peluso R, Iervolino S, Russolillo A, Lupoli R, Scarpa R and Ca RSG. Weight loss and achievement of minimal disease activity in patients with psoriatic arthritis starting treatment with tumour necrosis factor alpha blockers. *Ann Rheum Dis*. 2014;73:1157-62.

11. Gisondi P, Del Giglio M, Di Francesco V, Zamboni M and Girolomoni G. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. *The American journal of clinical nutrition*. 2008;88:1242-7.

12. Diguet N, Trammell SAJ, Tannous C, Deloux R, Piquereau J, Mougenot N, Gouge A, Gressette M, Manoury B, Blanc J, Breton M, Decaux JF, Lavery GG, Baczko I, Zoll J, Garnier A, Li Z, Brenner C and Mericskay M. Nicotinamide Riboside Preserves Cardiac Function in a Mouse Model of Dilated Cardiomyopathy. *Circulation*. 2018;137:2256-2273.

13. Hou Y, Lautrup S, Cordonnier S, Wang Y, Croteau DL, Zavala E, Zhang Y, Moritoh K, O'Connell JF, Baptiste BA, Stevnsner TV, Mattson MP and Bohr VA. NAD(+) supplementation

normalizes key Alzheimer's features and DNA damage responses in a new AD mouse model with introduced DNA repair deficiency. *Proceedings of the National Academy of Sciences of the United States of America*. 2018;115:E1876-E1885.

14. Martens CR, Denman BA, Mazzo MR, Armstrong ML, Reisdorph N, McQueen MB, Chonchol M and Seals DR. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD(+) in healthy middle-aged and older adults. *Nature communications*. 2018;9:1286.

15. Airhart SE, Shireman LM, Risler LJ, Anderson GD, Nagana Gowda GA, Raftery D, Tian R, Shen DD and O'Brien KD. An open-label, non-randomized study of the pharmacokinetics of the nutritional supplement nicotinamide riboside (NR) and its effects on blood NAD+ levels in healthy volunteers. *PloS one*. 2017;12:e0186459.

16. Canto C, Houtkooper RH, Pirinen E, Youn DY, Oosterveer MH, Cen Y, Fernandez-Marcos PJ, Yamamoto H, Andreux PA, Cettour-Rose P, Gademann K, Rinsch C, Schoonjans K, Sauve AA and Auwerx J. The NAD(+) precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. *Cell metabolism*. 2012;15:838-47.

17. Benyo Z, Gille A, Kero J, Csiky M, Suchankova MC, Nusing RM, Moers A, Pfeffer K and Offermanns S. GPR109A (PUMA-G/HM74A) mediates nicotinic acid-induced flushing. *The Journal of clinical investigation*. 2005;115:3634-40.

18. Dollerup OL, Christensen B, Svart M, Schmidt MS, Sulek K, Ringgaard S, Stodkilde-Jorgensen H, Moller N, Brenner C, Treebak JT and Jessen N. A randomized placebo-controlled clinical trial of nicotinamide riboside in obese men: safety, insulin-sensitivity, and lipid-mobilizing effects. *The American journal of clinical nutrition*. 2018;108:343-353.

19. Pozzilli P, Visalli N, Signore A, Baroni MG, Buzzetti R, Cavallo MG, Boccuni ML, Fava D, Gragnoli C, Andreani D and et al. Double blind trial of nicotinamide in recent-onset IDDM (the IMDIAB III study). *Diabetologia*. 1995;38:848-52.

20. Lampeter EF, Klinghammer A, Scherbaum WA, Heinze E, Haastert B, Giani G and Kolb H. The Deutsche Nicotinamide Intervention Study: an attempt to prevent type 1 diabetes. DENIS Group. *Diabetes*. 1998;47:980-4.

21. Trammell SA, Schmidt MS, Weidemann BJ, Redpath P, Jaksch F, Dellinger RW, Li Z, Abel ED, Migaud ME and Brenner C. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. *Nature communications*. 2016;7:12948.

22. Chi Y and Sauve AA. Nicotinamide riboside, a trace nutrient in foods, is a vitamin B3 with effects on energy metabolism and neuroprotection. *Current opinion in clinical nutrition and metabolic care*. 2013;16:657-61.