A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO ESTABLISH THE EFFICACY AND SAFETY OF ONCE WEEKLY ORAL AMINOPTERIN FOR THE TREATMENT OF SUBJECTS WITH MODERATE-TO-SEVERE PSORIASIS

Syntrix Protocol AMT-PSO-201

Protocol Version: 1.8
01 December 2018

Study Agent: LD-Aminopterin 0.5 mg tablets

Protocol Number: Syntrix-AMT-PSO-201

IND Number: 71,205

Sponsor: Syntrix Biosystems, Inc.

Personnel: Stuart Kahn, MD (Project Director, Sponsor's Medical Monitor)
James McNamara, MD (NIAID Medical Monitor and Independent Safety Monitor)
John Zebala, MD, PhD (Regulatory Affairs)
Matt Johnson, MS (Biostatistician)
Sandi Tennyson (Data Manager)
Aaron Schuler, PhD (Formulation Scientist)
Kristi Garrett (CMO Representative)

Contact Information

Clinical Site	**Principal Investigator**
Menter Dermatology Research Institute Baylor Medical Pavilion 3900 Junius Street, Suite 125 Dallas, Texas 75246 Tel: (972) 354-7993	Alan Menter, M.D. Tel: 972-354-7993 Email: alanmresearch@gmail.com
Dermatology Associates 1730 Minor Avenue, Suite 1000 Seattle, WA 98101-1498 Tel: (206) 267-2100 Fax: (206) 267-2101	Peter Jenkin, MD Tel: (206) 267-2100 Email: pjenkin@daseattle.com
Additional sites to be determined.	
Sponsor	
Syntrix Biosystems, Inc. 215 Clay Street NW Suite B5 Auburn, WA 98001 Fax: 253-833-8127	
Stuart Kahn Tel: 206-524-0214 Alt Tel: 253-833-8009 x32 Mobile: 206-330-7604 Email: skahn@syntrixbio.com	John Zebala Tel: 253-833-8009
Aaron Schuler Tel: 253-833-8009	Kristi Garrett Tel: 252-317-3996
NIH-NIAID	
Autoimmunity and Mucosal Immunity Branch Division of Allergy, Immunology and Transplantation NIAID, NIH 5601 Fishers Lane, 7D31 Rockville, MD 20852	James McNamara, MD Chief, Autoimmunity and Mucosal Immunity Branch Division of Allergy, Immunology and Transplantation Tel: (240) 627-3517 Email: jmcnamara@niaid.nih.gov
Statistician	
DF/Net Research Inc. 140 Lakeside Avenue, Suite 310 Seattle, WA 98122	Matt Johnson Tel: (206) 322-5931 Email: matt@dfnetresearch.com

Principal Investigator Agreement

Protocol Number: Syntrix-AMT-PSO-201

I, the undersigned, have reviewed this protocol, including all attached information.

I agree to conduct this clinical study in accordance with the E6 Guidance of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) "Good Clinical Practice: Consolidated Guidance", and the U.S. Code of Federal Regulations governing the protection of human subjects (21 CFR 50), Institutional Review Boards (21 CFR 56) and the obligations of clinical investigators (21 CFR 312). Furthermore, I agree to maintain all study documentation for the time specified in this protocol.

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Principal Investigator Signature

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Printed Name

_____

Date

Table of Contents

List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
API	Active Pharmaceutical Ingredient
BBB	Blood Brain Barrier
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats Per Minute
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
CRU	Clinical Research Unit
CRP	C-Reactive Protein
DAS	Dermatology Associates
DHFR	Dihydrofolate reductase
DSM	Data and Safety Monitoring
DSMB	Data and Safety Monitoring Board
EMA	European Medicines Agency
FDA	Food and Drug Administration
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIPAA	Health Assurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference for the Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intent-To Treat
LOCF	Last Observation Carried Forward
LOQ	Limit of Quantification

MDRI	Menter Dermatology Research Institute
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NDA	New Drug Application
NIAID	National Institute Of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protection
OHSR	Office for Human Subjects Research
PASI	Psoriasis Area and Severity Index
PE	Physical Exam
PHI	Protected Health Information
PI	Principal Investigator
PID#	Participant Identification Number
QA	Quality Assurance
QC	Quality Control
RR	Respiratory Rate
SAE	Serious Adverse Event
SID#	Screening Identification Number
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
sPGA	Static Physician Global Assessment
SSP	Study Specific Procedure
TBD	To be determined
TS	Thymidylate Synthase
WBC	White Blood Cell

Protocol Summary (Synopsis)

Protocol Number: Syntrix-AMT-PSO-201

Objectives:

The purpose of the study is to investigate the efficacy and safety of LD-AMT in adult subjects with moderate-to-severe psoriasis. LD-AMT is manufactured as a 0.5 mg tablets.

Primary Objective:

To determine the efficacy of LD-AMT in the treatment of subjects with moderate-to-severe psoriasis.

Secondary Objectives:

To determine the safety of LD-AMT in the treatment of subjects with moderate-to-severe psoriasis

Design:

A Phase 2, multi-center, randomized, double-blind, placebo-controlled study enrolling subjects with moderate-to-severe psoriasis to investigate the safety and efficacy of LD-AMT (3 mg (six 0.5 mg tablets overencapsulated in a single capsule). Forty-six subjects are randomized to one of two parallel treatment arms: LD-AMT (3 mg) or placebo, in a 1:1 ratio. The endpoint analysis will include efficacy and safety. Randomized subjects will initially enter a 14-week treatment phase, followed by a 6-week post-treatment phase.

Study Population:

Male and female subjects with moderate-to-severe psoriasis 18 years of age or older.

Sample Size and Randomization:

A total of 46 subjects will be enrolled, 23 in the LD-AMT treatment arm, and 23 in the placebo arm. Subjects will be randomly assigned to receive LD-AMT or placebo.

Main Inclusion Criteria:

Male or female subjects aged ≥18 years having a diagnosis of moderate-to-severe psoriasis for at least 6 months confirmed by a dermatologist, defined here as plaque-type psoriasis affecting a body surface area of ≥10% and a PASI of ≥10.

Study Duration:

Enrollment of 46 subjects is estimated to take approximately 18 months. Subjects will be on study for 20 weeks. It will take approximately 24 months to complete the study after enrollment of the first subject.

Endpoints:

Efficacy:

1. Proportion of subjects achieving Psoriasis Area and Severity Index of 75% (PASI 75) at study Day 98 (14 weeks).
2. Static Physician Global Assessment (sPGA) dichotomized to success or failure at study Day 98 (14 weeks).
3. Proportion of subjects achieving PASI 50 at study Day 98 (14 weeks).
4. Mean reduction in the PASI at study Day 98 (14 weeks).
5. Proportion of subjects achieving "success" in erythema at study Day 98 (14 weeks).
6. Proportion of subjects achieving "success" in scaling at study Day 98 (14 weeks).
7. Proportion of subjects achieving "success" in plaque induration at study Day 98 (14 weeks).

Safety: Adverse events.

Exploratory:

1. Mean hematologic (e.g., hemoglobin, platelets, leukocytes) and hepatic laboratory (e.g., SGOT, SGPT) values over the treatment-phase.
2. Fraction of abnormal hematologic and hepatic laboratory values over the treatment-phase.
3. Cumulative incidence of abnormal hematologic and hepatic laboratory values as a function of time over the 14-week treatment-phase.
4. Mitochondrial and cytoplasmic folate metabolism correlates with AMT efficacy and toxicity.

Monitoring:

Syntrix Biosystems and its representatives.

Clinical Sites:

Menter Dermatology Research Institute, Dallas, Texas
Dermatology Associates, Seattle, WA
Additional sites to be determined.

Sponsor:

Syntrix Biosystems, Inc.

1 OBJECTIVES

The purpose of this study is to determine the efficacy and safety of a new drug to treat psoriasis, LD-AMT. LD-AMT 3.0 mg is administered as a once weekly oral dose to adult subjects with moderate-to-severe psoriasis.

1.1 Primary Objective

To evaluate the efficacy of once weekly 3.0 mg oral LD-AMT administered for 14 weeks in this double-blind, placebo-controlled, trial.

1.2 Secondary Objectives

- To assess the safety of once weekly 3.0 mg oral LD-AMT administered for 14 weeks.
- To assess the relationship of each subject's level of expression of cytoplasmic and mitochondrial folate metabolism genes to the subject's psoriasis treatment efficacy and safety outcomes.

2 BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Introduction

Psoriasis is a common papulosquamous skin disease that may be associated with a seronegative spondyloarthropathy. Psoriasis affects 2% of the US population, and approximately 10% of these subjects have psoriatic arthritis. Psoriasis has two peaks of onset, one in adolescents and young adults (at 16 to 22 years of age), and the other in older persons (at 57 to 60 years of age), but the range extends from newborn to 100 years. Men and women are affected equally, but women may be affected earlier than men.

US primary care physicians initially see 58% of the estimated 150,000 – 260,000 new cases of psoriasis per year, but dermatologists handle 80% of the 3 million office and hospital visits for psoriasis each year (Stem '96).

Experts agree that psoriatic skin lesions are the result of inflammation in the dermis and epidermal hyperproliferation with abnormal differentiation. The primary pathologic process is believed to arise in the immune system, specifically dysregulation of activated T-cell interactions with antigen-presenting cells and overproduction of proinflammatory cytokines. Evidence for this theory derives from the dramatic improvement of severe psoriasis in subjects treated with immunosuppressive drugs used in organ transplantation, such as cyclosporine and tacrolimus.

Although a single disease, psoriasis has several morphologic expressions and a full range of severity. The form that psoriasis takes in a subject depends on a combination of genetic influences, environmental factors (e.g., trauma and climate), associated diseases (especially infections), and concomitant medications. Certain drugs, including lithium, antimalarials, beta-adrenergic blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and interferons, have been reported to induce psoriasis or aggravate preexisting disease in some subjects. Emotional stress

may also cause cutaneous nerve fibers to release peptides. This can evoke inflammation or proliferation, thereby leading to a flare of psoriasis.

Over the past 25 years, methotrexate (MTX) has become a reference standard in the treatment of psoriasis. When used for the treatment of psoriasis, MTX inhibits the enzymes involved in purine metabolism, which leads to an accumulation of extracellular adenosine, a powerful anti-inflammatory autocoid, and the induction of T cell apoptosis (Cronstein '93; Genestier '98; Morabito '98; Paillot '98; Johnston '05).

Despite the effectiveness of MTX in treating moderate-to-severe plaque psoriasis, a randomized observer-blinded study demonstrated that 15 mg/wk oral monotherapy for 16 weeks in 43 subjects (given in three divided doses with a 12 hour interval between doses) did not achieve PASI 50 in 30% of subjects, and failed to achieve remission (i.e., > PASI 90) in 60% of subjects (Heydendael '03). The limited response and large interindividual variability in anti-psoriatic effect of oral MTX has been attributed to marked differences in oral bioavailability between subjects, where a poor reduction in PASI score has been significantly correlated to poor oral bioavailability of MTX (Chladek '98; Chladek '02; Chladek '05). While some of these subjects may still respond to subcutaneous MTX, development of alternative, more efficacious antifolates, with increased and less variable oral bioavailability, is urgently needed.

Additionally, up to 30% of subjects with moderate-to-severe plaque psoriasis discontinue oral MTX primarily because of intolerance to the drug (Haustein '00). Common side effects include GI toxicity (nausea, anorexia, stomatitis), marrow suppression and hepatotoxicity. The latter is of particular concern in psoriatic subjects, who may develop life-threatening cirrhosis after chronic use. Depending on the dosage of oral MTX, reports indicate that 10-47% of subjects with psoriasis also experience a variety of CNS effects including headache, fatigue, lethargy, disorientation, poor memory and agitation (Nyfors '78; Duller '85; Haustein '00; Wollina '01).

Thus, an important goal is to develop newer antifolate agents that can increase the proportion of subjects that can be maintained at an orally efficacious dose level with less treatment-related toxicity.

2.2 Description of the Study Agent

The study agent is the Sponsor's scored biconvex 0.5 mg LD-aminopterin tablets. Aminopterin (AMT; 4-amino-pteroylglutamic acid, aminopterin is the International Nonproprietary Name 'INN' for the sodium salt) is an antifolate in the same class as methotrexate (MTX; 4-amino-N10-methyl-pteroylglutamic acid, also known as amethopterin, see FIG. 1). Compared to other antifolates, AMT bears the closest structural similarity to folic acid, differing from the natural substrate by only two atoms.

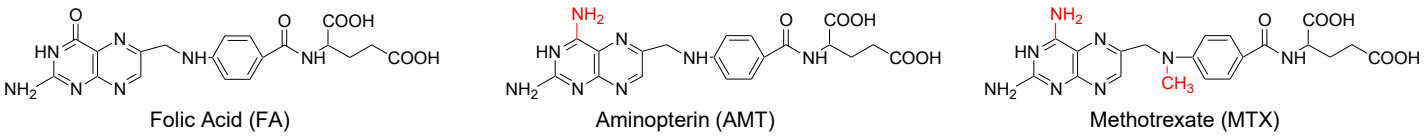

FIG. 1. The structure of folic acid (FA), AMT, and MTX. AMT, first synthesized in 1946 by Lederle Laboratories, was the first antifolate to exhibit efficacy in pediatric ALL reported in 1948 by Sydney Farber (Farber '48). Structurally related antifolates, including MTX, were described by Lederle in the ensuing years from 1948 to 1955.

AMT was marketed by Lederle Laboratories between 1953 and 1964 as a 0.5 mg tablet for the indication of pediatric acute leukemia. It was used off-label to treat over 3,500 psoriatic subjects over its 11 year marketed period, being preferred over MTX by dermatologists of the time (Rees '64). Lederle discontinued marketing AMT for what appeared to have been manufacturing preferences for MTX. During the period of their use, the relative toxicity of AMT and MTX were never carefully examined by modern clinical trial standards.

Our more recent preclinical and clinical studies comparing AMT and MTX that are summarized in the sections that follow, indicate that AMT: (a) has improved mean oral bioavailability (>90%), (b) is more actively and completely taken up by cells, (c) accumulates less in the CSF, (d) spares erythropoiesis in the marrow, and (e) spares the liver as measured by liver transaminases.

These features have spurred renewed interest in testing AMT in the treatment of psoriasis, as well as in a variety of other autoimmune conditions where MTX is used ubiquitously; for example, in rheumatoid arthritis, transplantation (solid organ, GVHD), polymyositis, and uveitis to name a few. Thus, the results of clinical testing of AMT in psoriasis promise to have far reaching implications across clinical disciplines in addition to dermatology.

2.3 Relevant AMT Pre-clinical Studies

2.3.1 Adenosine Release In Vitro

Interactions between T cells, antigen presenting cells and keratinocytes play a key role in the pathogenesis of psoriasis (Prinz '99; Gudjonsson '04), and a continuous recruitment of mononuclear leukocytes is probably required for maintaining active psoriatic lesions (Davison '01). The inhibition of enzymes involved in purine metabolism by antifolates lead to the extracellular release of adenosine, a powerful anti-inflammatory autocoid that decreases the activation of antigen-stimulated cells, decreases the expression of adhesion molecules, and possibly induces T cell apoptosis (Cronstein '93; Genestier '98; Morabito '98; Paillot '98; Johnston '05).

Cronstein et al. reported that MTX induced adenosine release from fibroblasts in culture with an EC50 of 1 nM (Cronstein '91). Similarly, L-AMT caused a dose-dependent release of adenosine in cultured ma10[4] cells with an EC_{50} of 0.5 nM (data not shown). These data argue that the anti-inflammatory mechanism of both AMT and MTX is adenosine release.

2.3.2 Mouse Anti-Inflammatory Studies

L-AMT has been shown to be active in the murine air-pouch model of inflammation, and using this model we have quantified the dose-response relationship of L-AMT and L-MTX (Alcaraz '06). The activities of L-AMT and L-MTX were assessed by giving mice (5 CDI Swiss males per dose cohort) four weekly intraperitoneal injections of vehicle, or varying doses of L-AMT or L-MTX over the course of a month. L-AMT and L-MTX diminished, in a dose-dependent fashion, the number of leukocytes (predominantly neutrophils) that accumulated in the carrageenan-treated air pouches with EC_{50} values of 0.0009 mg/kg/wk and 0.04 mg/kg/wk, respectively ($p < 0.001$) (Alcaraz '06). Thus, using a once-weekly dosing regimen that mimics the clinical L-MTX regimen

employed in RA and psoriasis, L-AMT is a 43-fold more potent anti-inflammatory agent than L-MTX.

The dose of L-MTX required to achieve a 50% to 100% response in the air pouch model is similar to the dose required clinically for the treatment of RA or psoriasis (the equivalent of 7-25 mg/week in a 70-kg individual), arguing that the model is a valid indicator of antifolate potency in humans. Based on the dose-response in mice, we predict that the appropriate clinical dose range of L-AMT for treating humans with inflammatory disorders will range from 0.1-2.0 mg/week in a 70-kg individual, which is encompassed by the doses used in this RA study (3.0 mg LD-AMT which contains 1.5 mg L-AMT), and is several-fold below the known human maximally tolerated weekly dose where mucositis becomes dose-limiting (i.e., ~3-7 mg/week L-AMT). The weekly AMT dosing interval to be used in this study is by the MTX regimen employed in RA and psoriasis. Early human experience with the Lederle tablet further supports these conclusions, where relapse of psoriatic lesions after discontinuation of L-AMT was usually seen after 2 weeks (range 2-8 weeks); (Rees '55; Rees '59).

The greater potency of AMT over MTX is mainly due to a greater efficiency of cell uptake of L-AMT from plasma (Sirotnak '75; Fry '82; Fry '83). Surprisingly, under these same dosage conditions, the brains of L-AMT-treated animals contained significantly less L-AMT than the brains of L-MTX-treated animals ($P \leq 0.0003$), consistent with transport of antifolate across the blood-brain barrier (BBB) being a concentration dependent phenomenon in mice (Cole '06). These findings in mice paralleled our findings in humans, where weekly doses of 4.0 mg/m^2 L-AMT and 100 mg/m^2 L-MTX produced equivalent levels of each drug in erythrocytes, but significantly less AMT in the CSF of human subjects ($p < 0.0001$, two-tailed t-test) (Cole '06). This difference in the distribution of L-AMT and L-MTX into brain parenchyma and CSF is the basis for the clinical hypothesis that AMT may decrease the frequency or severity of antifolate-related neurotoxicity by sparing the brain, while providing equivalent systemic anti-inflammatory efficacy as MTX.

2.3.3 L-AMT and D-AMT Pharmacokinetics and Toxicity in Dogs

The oral pharmacokinetics and toxicity of L-AMT and D-AMT were evaluated in 40 beagle dogs in escalating doses (Menter '12). The L-enantiomer dose range was 0.02 to 2.4 mg/kg, and the D-enantiomer dose range was 0.8 to 82.5 mg/kg. Doses of the L-enantiomer ranged from a dose having optimal anti-inflammatory activity at the low end of the range (data from canine model of inflammation), to the minimum lethal single dose at the upper end of the range (Thiersch '49; Rieselbach '63). Doses of the D-enantiomer were at least 10-fold larger than the L-enantiomer doses to allow for possible poor intestinal absorption of the D-enantiomer. The C_{max} of L-AMT was 11- and 6-fold larger than the C_{max} of D-AMT at doses of 0.8 and 2.5 mg/kg, respectively ($p < 0.001$). The $AUC_{(0\text{-}4\ h)}$ of L-AMT was 12- and 6-fold larger than the $AUC_{(0\text{-}4\ h)}$ of D-AMT at doses of 0.8 and 2.5 mg/kg, respectively ($p < 0.001$). There was no dose-dependent trend in T_{max} for either L-AMT or D-AMT, and no significant difference between the T_{max} values for L-AMT and D-AMT.

Maximum plasma concentration and observed area under the curve were dose-proportional over the L-AMT dose range of 0.02 to 0.2 mg/kg and the entire tested D-AMT dose range of 0.8 to 82.5 mg/kg. The same pharmacokinetic parameters responded non-linearly to L-AMT doses above 0.2 mg/kg. As reflected by the 6- to 12-fold larger maximum plasma concentration and observed area

under the curve of L-AMT compared to D-AMT at identical doses, the exposure is stereoselective for the L-enantiomer. Non-linearity in pharmacokinetic parameters as a function of L-AMT dose, and stereoselectivity for L-AMT over D-AMT together indicate a transporter-mediated component in absorption.

The toxicity of L-AMT and D-AMT was evaluated in each of the above 40 beagle dogs as function of dose through detailed daily clinical and physical observations, and terminal necropsy that included gross and histopathologic examinations (Menter '12). An additional vehicle group of 4 beagle dogs served as a negative control. Beginning three days after the oral administration of L-AMT, dogs in the 0.8 and 2.5 mg/kg dose groups exhibited severe lethargy, anorexia, vomiting, weight loss, and diarrhea (including bloody) characteristic of acute antifolate intoxication, with one dog found dead and another found moribund and euthanized. Dogs in the 0.2 mg/kg L-AMT dose group exhibited diarrhea five days after dosing. Dogs in the remaining 0.02 and 0.08 mg/kg L-AMT dose groups exhibited no signs of clinical antifolate toxicity. At necropsy, dogs in the 2.5 mg/kg L-AMT dose group were found to have multiple red and pigmented lesions throughout the small and large intestines that consisted of epithelial necrosis and neutrophilic inflammation on histologic examination. Other histopathologic changes in the 2.5 mg/kg L-AMT dose group consisted of mild to moderate bone marrow hypocellularity. Dogs in the remaining L-AMT dose groups (lower doses) had no significant gross lesions or histopathologic findings at necropsy. Although the largest D-AMT dose (82.5 mg/kg) was 100-fold greater than the minimum lethal L-AMT dose (0.8 mg/kg) and yielded a 7-fold greater exposure in the plasma, none of the D-AMT dose groups exhibited any signs of clinical toxicity and there were no significant gross lesions or histopathologic changes at necropsy (Menter '12).

In summary oral absorption was stereoselective for the L-enantiomer and D-AMT was not toxic at the maximum dose tested (82.5 mg/kg), which was 100-fold larger than the minimum lethal L-AMT dose (0.8 mg/kg) (Menter '12).

2.3.4 Canine PK Study

For treatment of inflammatory diseases the Sponsor had prepared a 0.25 mg tablet (investigational batch 157I0907) that contained racemic LD-AMT. For oncology treatment and use in previous oncology studies, the Sponsor prepared a 1 mg tablet (investigational batch 116I0604) that contains > 99% L-AMT. Therefore, the Sponsor performed a study in Beagle dogs to compare the toxicology and toxicokinetics of these two AMT formulations (Menter '12). The study design was a randomized, single dose, two-period cross-over study to compare 0.25 mg LD-AMT tablet with a 1.0 mg reference AMT tablet (L-isomer). Ten dogs were randomized to two parallel arms (5 per arm) to ingest a 1.0 mg single dose of either the 0.25 mg tablets (4 x 0.25 mg tablets) or the reference 1.0 mg tablet (1 x 1.0 mg tablet), and blood specimens were obtained from each dog over 12 hours. Seven days later dogs of both arms were crossed-over and received a single oral 1.0 mg dose of the other formulation and again blood specimens were obtained over 12 hours. The endpoint analysis included safety, and measurement of the L and D isomers in plasma by chiral LC/MS.

There were no significant AEs, including an absence of gastrointestinal AEs which are the earliest symptom of antifolate intoxication. The concentration profiles of L-AMT in the plasma samples following ingestion of the two test formulations (L-AMT formulation and LD-AMT

formulation) were indistinguishable. Importantly, following ingestion of the LD-AMT formulation, no D-AMT was detected in any plasma sample. Therefore, following ingestion of the LD-AMT formulation, D-AMT was not absorbed. Combined, these findings demonstrate that LD-AMT is toxicologically and toxicokinetically indistinguishable from L-AMT, and that the oral administration of the LD-AMT does not result in detectable systemic exposure to D-AMT (Menter '12).

2.3.5 Canine Atopic Dermatitis (CAD) Pilot Study

CAD is a chronic, progressive allergic skin disease that results in a profound impairment of quality of life due to persistent itching, spontaneous and self-induced skin lesions, secondary skin infections, and loss of sleep. It is associated with IgE antibodies to environmental allergens (Olivry '01).

In an initial 4-week open-label pilot trial, followed by an optional 1-year extension, AMT treatment of CAD was safe and effective (Olivry '07). The Sponsor's 1 mg L-AMT tablet (investigational batch 116I0604) was used to treat adult mongrel outpatient dogs with CAD at North Carolina State University. Subjects were given L-AMT orally at 0.010 mg/kg/week for weeks 1-4 (except for one subject who was given 0.015 mg/kg/week at week 4 because of lack of efficacy); and escalated as needed to 0.015 or 0.020 mg/kg/wk during the 1-year extension.

All 8 dogs that completed the initial 4-week efficacy phase entered the extension phase. Four (50%) completed 16 weeks or more of AMT therapy (mean 19.6 weeks, range 8-40 weeks). Seven subjects were evaluable for efficacy during the extension phase. The overall efficacy in CAD was impressive. At week 20 for example, all dogs exhibited a greater than 50% reduction in their disease assessments, and 66% had greater than a 90% reduction in their disease assessments. No adverse events were observed in any subjects treated for up to 40 weeks with doses up to 0.02 mg/kg/week, a dose equivalent to 1.5 mg/week L-AMT in a 70-kg human.

Together these data indicate that the potency of L-AMT anti-inflammatory activity is similar across these species (mice, rats, dogs and humans). It is therefore reasonable to predict that 0.25-2.0 mg/week L-AMT in a 70-kg individual will be the appropriate clinical dose range for treating human inflammatory disorders. This is a dose range that is used in this psoriasis study and whose safety is supported by both animal and human studies.

2.3.6 CAD Dose Ranging Trial

Following the successful CAD pilot study, Syntrix sponsored (with support from NIH, National Institute of Arthritis and Musculoskeletal Diseases) a multi-center double-blinded, placebo-controlled, dose-ranging study randomizing 75 dogs to 5 parallel arms (15 subjects per arm). All 5 arms receive twice weekly oral dosing (one of the two weekly doses in 3 of the 5 arms is a dummy placebo dose). Thus, three arms receive once weekly LD-AMT at 0.01 mg/kg, 0.02 mg/kg or 0.03 mg/kg, and once weekly placebo. One arm receives twice weekly LD-AMT at 0.01 mg/kg, and one arm receives twice weekly placebo. Primary outcome efficacy was assessed at study Day 84 (end of 12 weeks). The Sponsor's 0.25 mg LD-AMT tablet (investigational batch 157I0907) was used.

Measures of toxicity were physical examination, and CBC and blood chemistry tests at Days 14, 35, 56 and 84. Seventy-five subjects completed the study; no safety concerns occurred. Efficacy was demonstrated in the 0.02 mg/kg/week dose arm (published in Zebala JA, Mundell A, Messinger L, Griffin CE, Schuler AD, Kahn SJ. LD-aminopterin in the canine homologue of human atopic dermatitis: a randomized, controlled trial reveals dosing factors affecting optimal therapy. *PLoS One*. 2014 Sep 25;9(9):e108303).

2.4 Relevant Human AMT Clinical Studies

2.4.1 Psoriasis Subjects Exposed to Lederle's L-AMT 0.5 mg Tablet

In the 1950s Lederle produced a 0.5 mg L-AMT tablet. Safety data were available on 579 human subjects with psoriasis treated with this Lederle tablet. The extent of L-AMT exposure was under 1 year in 472 subjects (81.5%), 1-5 years in 87 subjects (15.0%), and 10 years in 20 subjects (3.5%). An additional 3,738 psoriasis subjects were exposed to AMT monotherapy with the Lederle L-AMT tablet for periods not specified in the primary literature reports, indicating a total of 4,317 psoriasis subjects were exposed to at least one course of Lederle's L-AMT tablet.

2.4.2 Oncology Subjects Exposed to AMT in Multi-Agent Therapy (CINJALL trial)

Between March 2001 and September 2005, 58 children or young adults with acute lymphoblastic leukemia (ALL) enrolled in CINJALL: A Phase IIB Trial Of AMT In Multiagent Therapy For Children With Newly Diagnosed Acute Lymphoblastic Leukemia at High Risk of Relapse. The CINJALL trial used the Sponsor's 1 mg L-AMT tablet (investigational batch 116I0604). The extent of exposure was a median of 98 weeks (range 12 to 140 weeks, N=32 subjects) or 2,800 subject-weeks.

The CINJALL trial employed adult-equivalent doses of AMT (3.6-7.2 mg per week) and MTX (77-180 mg per week). Once-weekly MTX doses in RA and psoriasis range from 7.5-30 mg (15-20 mg usually), but may extend in some select subjects to 50 mg per week. The upper MTX range employed in RA and psoriasis subjects thus approaches the lowest MTX dose employed in CINJALL.

AMT was found to be 20- to 25-fold more potent than MTX in CINJALL based on a variety of toxicity measures. Using this potency ratio, the equipotent anti-inflammatory dose range for AMT can be extrapolated from the known anti-inflammatory MTX dose range. This extrapolation results in a predicted once-weekly range of 0.3-1.5 mg for L-AMT, and 2.0 mg occasionally.

As CINJALL AMT and MTX doses were up to 6-fold greater than one would typically use for anti-inflammatory indications, the rate and severity of toxicities related to AMT and MTX were accelerated, and this study afforded the opportunity to compare AMT and MTX toxicity over 2-years of subject exposure and demonstrated the potential advantages of AMT over MTX when used at lower anti-inflammatory doses.

2.4.2.1 Hematologic Sparing

Treatment for over 50 weeks with L-AMT 2 mg/m^2 (3.6 mg/week in an average adult) caused equal suppression of granulopoiesis to L-MTX 40 mg/m^2 (72 mg/week in an average adult), but resulted in significantly less suppression of erythropoiesis as measured by mean hemoglobin levels ($p < 0.001$).

Contemporary experience with MTX in psoriasis provides a useful benchmark for comparison with AMT. In 2001, Wollina et al. reported the chronic toxicities of MTX in 81 subjects with psoriasis and psoriatic arthritis treated with 6.5-40 mg MTX once per week for about 100 weeks (Wollina '01). There were 32 anemic events, the CTC grades were as follows: 4 were grade 1, 24 were grade 2 (most common), 3 were grade 3, and 1 was grade 4. AMT therefore offers the potential to make an important clinical improvement in the incidence or severity of anemia AEs.

2.4.2.2 Hepatic Sparing

The potential for MTX to cause hepatotoxicity and cirrhosis in psoriasis (Roenigk '98) and RA (Kremer '94) subjects has been recognized for decades, and has been extensively discussed and studied in the literature. Both dermatologists and rheumatologists monitor for liver toxicity by performing regular liver blood tests (ALT and AST). The presumed mechanistic model of MTX-mediated liver injury and corresponding changes in liver blood tests is through intermittent episodes of hepatocellular necrosis, which in turn result in intermittent rises in serum AST above the normal range. The greater the frequency of the necrosis, the greater probability that liver fibrosis, and uncommonly cirrhosis, will occur. In a study by Kremer et al. of 354 baseline and annual sequential liver biopsies in 94 RA subjects administered oral L-MTX 15 mg per week, it was shown that the mean AST and the frequency of abnormal AST values significantly increased in subjects as a function of the Roenigk grade, consistent with the mechanistic model (Kremer '96). The maximum magnitude of abnormal AST values did not correlate with histologic grade. The difference in the frequency of abnormal AST elevations between Roenigk Grade I and IIIA was 8.7% vs. 18.6%, respectively.

In CINJALL, oral L-AMT 3.6 mg/week in an average adult and L-MTX 72 mg/week in an average adult both resulted in elevations of AST: this happened in 24.4% of the AMT arm, and 56.6% of the MTX arm ($p = 0.0001$, Fisher's exact test). The AMT arm also had a significantly lower mean value for all AST measurements over the same period ($p = 0.0001$). AMT thus appears to exhibit clinically relevant sparing of the liver compared to MTX, both in terms of the frequency and the mean value of AST elevations.

2.4.3 CNS Sparing Relative to Systemic Compartments

Neurotoxicity arising during weekly administration of MTX in RA and other autoimmune diseases manifests as headache, fatigue, somnolence, vertigo and uncomfortable dissociative-type experiences (i.e., the "post-dosing reaction"). This neurotoxicity is presumed to be mediated by binding of MTX within the CNS to high-affinity intracellular targets such as DHFR. Penetration of AMT and MTX across the blood-brain barrier is thought to be concentration dependent. Indeed, of 41 psoriatic subjects treated with MTX, the 9 subjects who experienced headache on the day of MTX administration had plasma MTX C_{max} of 0.76 ± 0.28 µM, whereas those subjects without headache had plasma MTX C_{max} of 0.24 ± 0.15 µM (Chladek '05).

During CINJALL CSF was collected for analysis of antifolate concentrations. These date demonstrated that CSF MTX concentrations (mean ± SE = 26.3 ± 5.0 nM; n = 45) were significantly greater than CSF AMT concentrations (3.56 ± 0.83 nM; n = 64; P<0.0001, two-tailed t-test) (Cole '06). These data indicate that the penetration of the blood-brain barrier by AMT and MTX are concentration dependent. Because AMT is 20- to 25-fold more potent than MTX in the periphery, lower plasma concentrations of AMT result in lower CSF concentrations, and thus lower CNS intracellular AMT. As a result of these differences in CNS intracellular concentrations of AMT and MTX, AMT may cause less neurotoxicity when used in autoimmune indications (Cole '06).

2.4.4 Oncology Subjects Exposed to AMT Monotherapy

AMT monotherapy (Lederle's L-AMT) exposure was reported in 218 subjects. The exposure periods reported were 0-12 weeks in 178 subjects (81.73%), 13-28 weeks in 24 subjects (11.0%), 29-44 weeks in 13 subjects (5.9%), 45-60 weeks in 1 subject (0.45%) and 61-76 weeks in 2 subjects (0.92%). An additional 277 oncology subjects were exposed to L-AMT monotherapy (using Lederle's L-AMT) for periods not specified in the primary literature reports, providing for a total of 495 oncology subjects exposed to L-AMT monotherapy.

2.4.5 AMT Efficacy Experience in Psoriasis

Two studies with the Lederle L-AMT tablet compared L-AMT and L-MTX (active control) using each drug in an equivalent dosing regimen (Rees '61; Strakosch '63). The Rees et al. study used a crossover design (n=37 in AMT and MTX arms), and the Strakosch study used a parallel dose group design (N=84 AMT, N=36 MTX). Both studies found that 3.0-6.0 mg/wk L-AMT produced significantly ($P < 0.001$ both studies, Fisher's, two-tailed) more successes than L-MTX at a 5-fold greater dose. Analyses of these studies revealed the important observation that increasing dose intensity in L-AMT monotherapy beyond about 1.5 mg/wk (given in 3 divided doses over 3 days) was associated with an increased incidence of AEs, but no increase in therapeutic successes.

2.4.6 Early (1951) AMT Efficacy Experience in RA

As was the case in cancer, the first reported use of an antifolate to treat RA employed L-AMT, not L-MTX (Ward '85). In 1951, Gubner et al. described the use of L-AMT to treat RA in six patients (Gubner '51). They noted a rapid improvement in arthritis in 5 patients, with exacerbation 1-6 weeks after stopping treatment. Patients were given 1-2 mg of L-AMT daily, and stomatitis developed in 5 of the patients within 1 to 2 weeks. Other adverse effects were nausea, diarrhea, and alopecia.

It is now appreciated that the dose employed by Gubner et al. was 2- to 4-fold above the MTD for L-AMT, and at least 7- to 14-fold above the dose predicted to be efficacious in a patient with RA. This study provides evidence that L-AMT is active in RA. To facilitate comparing the the efficacy of L-AMT and L-MTX, we retrospectively evaluated the degree of Gubner's reported improvement using modern ACR criteria. We found significant improvements in tender joints, swollen joints, and physician's global score of a magnitude similar to those reported for L-MTX (Hoffmeister '72; Wilke '80; Wilkens '80; Hoffmeister '83; Thompson '84; Weinblatt '85; Kremer '86; Weinblatt '88; Weinblatt '90; Choi '00; Sokka '02; Ruperto '08). Gubner et al. is the only report

in the literature of the use of L-AMT to treat RA, and represents a historical landmark often cited in reviews describing the development of L-MTX for RA. A review by Ward notes that the observation by Gubner et al. went unnoticed for 20 years for a variety of reasons until it was rediscovered in 1972 when the first clinical use of L-MTX in RA patients was reported (Ward '85). As L-AMT manufacturing by Lederle was discontinued in 1965, L-MTX became the inevitable antifolate of choice for a variety of diseases including RA.

2.4.7 AMT Chronic (> 1 year) Toxicity Experience in Psoriasis and Oncology

The most common AEs associated with chronic AMT therapy include mucositis, bone marrow suppression (usually manifesting as leukopenia and thrombocytopenia), nausea, and abdominal discomfort. These can arise at any time during therapy. The incidence and severity of AEs generally exhibits a dose-response relationship. However, the schedule of administration can also influence toxicity, with divided weekly regimens, compared to once weekly regimens, increasing toxicity, presumably due to prolongation of DHFR suppression in normal tissues. There is no evidence that the incidence of toxicity is related to the duration of treatment, cumulative dose or efficacy outcomes.

In all pooled data from clinical trials in psoriasis (N=427) employing 3-6 mg/week L-AMT given in divided daily doses, leukopenia (defined as WBC <3500/mm3) was seen in 4 subjects, but this was never greater than grade 2. No leukopenia was seen in 21 patients treated chronically with 1.5 mg/wk L-AMT in a divided dose regimen. In this protocol all doses are being given as a single weekly dose (i.e., less intense than divided doses), and therefore no grade 3 or 4 hematologic toxicities are anticipated. It is possible that grade 1 or grade 2 hematologic toxicities may occur uncommonly to rarely at the dose of 1.5 mg/wk L-AMT (3.0 mg LD-AMT).

2.4.8 Bioavailability

In psoriasis poor responses to MTX have been correlated to poor oral bioavailability (Chladek '98; Chladek '02; Chladek '05). Furthermore, the oral bioavailability of L-MTX in adults has been reported to be limited by intestinal absorption at doses above about 15 mg (Bannwarth '96). Thus, MTX non-responders cannot simply increase the MTX dose. In contrast to MTX, AMT oral absorption does not appear to be limited. If bioavailability is a limiting variable for oral MTX efficacy, then oral AMT may offer a greater response rate than oral MTX.

2.4.9 Syntrix LD-AMT Tablets in PK Study in Psoriasis Subjects

Syntrix sponsored a PK study in human subjects with psoriasis (ClinicalTrials.gov Identifier: NCT00937027) (Menter '12). The study was performed at the Dermatology Research Clinic of the Baylor Research Institute (Dallas, Texas, USA) and used Syntrix's 0.25 mg tablet (composed of LD-AMT; investigational batch 157I0907) and 1.0 mg tablet (composed of L-AMT; investigational batch 116I0604). The objective of the study was to compare the toxicology and toxicokinetics of these two AMT formulations. The study design was a randomized, single oral dose, two-period cross-over study to compare 0.25 mg AMT tablet (LD-AMT) with a 1.0 mg reference AMT tablet (L-isomer). Twenty-two subjects were randomized to two parallel arms (11 per arm)) to ingest a 1.0 mg single dose of either the new LD-AMT 0.25 mg tablets (4 x 0.25 mg tablets) or the reference

tablet L-AMT (1 x 1.0 mg tablet), and blood specimens were collected from each subject for 12 hours. Seven days later subjects of both arms crossed-over and received a single oral 1.0 mg dose of the other formulation and again blood specimens were collected over 12 hours. The endpoint analysis included safety and the AUC, Cmax and Tmax of L-AMT based on adverse events and L-AMT concentration in the blood following administration of either formulation. In addition, PK bioequivalence of the LD-AMT and L-AMT was analyzed.

The PK results demonstrated that the LD-AMT and L-AMT formulations were bioequivalent. Furthermore, absorption of LD-AMT was stereoselective for the L-isomer. The safety evaluation demonstrated that all AEs were grade 1 or grade 2. All adverse events related to the test study drug were expected. The study conclusions are that the LD-AMT was bioequivalent to the L-AMT. Absorption of aminopterin enantiomers was stereoselective for the L-isomer. The safety database for L-AMT tablets can be extrapolated to LD-AMT tablets (Menter '12).

2.4.10 Syntrix LD-AMT Tablets in Phase 2 Study in RA Subjects

The Sponsor completed a phase 2 trial (ClinicalTrials.gov Identifier: NCT01724931) that enrolled 175 MTX-naïve subjects with RA into a 12-week double-blind placebo-controlled LD-AMT dose ranging study. Subjects with active RA (≥ 6 tender and ≥ 6 swollen joints (28 joint count)) were randomized to one of three treatments: placebo, LD-AMT (1 mg), or LD-AMT (3 mg) in a 1:1:1 ratio. The primary efficacy endpoints were ACR20 and HAQ at Study Day 84 evaluated for each cohort in a sequential gate-keeping/step-down approach. Secondary endpoints included ACR20 (at Study Day 28), ACR50, ACR70, ACR-N, DAS28, DAS28 <3.2, DAS28 <2.6. Safety endpoints were all AEs, SAEs and treatment-emergent AEs (TEAEs), including laboratory measurements of serum chemistry and hematology, and the occurrence of dose limiting toxicity (i.e., interruption of dosing due to AEs as defined in protocol Section 8.7). PK analysis was performed on 90 of the enrolled subjects.

The 3.0 mg L/D-aminopterin significantly reduced disease activity by 12 weeks as measured by ACR20 (P=0.021), ACR-N (P=0.030) and DAS28 (P=0.009). The 1.0 mg dose did not reach significance. Blinded placebo-controlled safety data were obtained and confirm the safety of investigating 3 mg L/D-aminopterin according to this protocol (see IB).

2.5 Potential Risks and Benefits

Potential risks at the dose of LD-AMT to be used include those side-effects commonly known to be associated with antifolate use, such as stomatitis, hepatotoxicity, marrow toxicity, and more rarely pulmonary toxicity. The side-effects from LD-AMT are qualitatively equivalent to the side-effects arising from oral L-MTX therapy, which is the standard-of-care, that enrolled subjects might be offered.

The value of the information to be gained outweighs the potential risks involved. The ultimate availability of LD-AMT to subjects with psoriasis will be beneficial, as an alternative to L-MTX, with fewer anticipated toxicities. LD-AMT will also provide a low cost oral medication compared to the more expensive anti-cytokine therapies (e.g., etanercept, infliximab, adalimumab).

The subjects enrolled in the study can also expect greater LD-AMT bioavailability and thus a greater proportion of subjects experiencing clinical improvement. In addition, subjects enrolled in the study may also benefit from more careful monitoring of their disease status than what is provided under standard-of-care. Subjects enrolled may also benefit from greater fewer treatment emergent toxicities than might occur with MTX.

2.6 Rationale

Lederle marketed L-AMT tablets from 1953 to 1964, and L-MTX tablets from 1955 to the late 1990s. The major published studies conducted to evaluate the efficacy of AMT in psoriasis were open-label. These studies showed a significantly greater number of treatment successes with AMT than MTX and showed that approximately 55-65% of a population will reach success after AMT treatment. This protocol is designed to conduct a placebo-controlled double-blinded trial to determine if LD-AMT is efficacious and safe in the treatment of subjects with moderate-to-severe psoriasis who are naïve to prior MTX treatment.

The 14 week duration was selected as subjects treated with MTX reach maximum improvement in PASI score by 14 weeks (Heydendael '03). Similarly, the time to onset of psoriasis lesion "clearing" or "almost clearing" in early pilot trials with AMT support 14 weeks as sufficient to observe the majority of the maximum efficacy. Hence a 14-week treatment duration was chosen. Thus 14 weeks will allow responders to declare themselves, and non-responders to be treated within the ethical limits established in previous trials for placebo treatment.

The weekly dose of LD-AMT for this study is 3.0 mg (1.5 mg of L-AMT). The selection of this dose for efficacy purposes is based on preclinical studies, human studies, and the known relative potencies of AMT and MTX. AMT is an antimetabolite that is associated with a variety of dose-dependent toxicities qualitatively similar to those seen with MTX. In 1998 our phase I oncology trial determined the MTD, the dose at which the mildest symptoms first appear, of AMT to be 0.13 mg/kg/week (with no folic acid supplementation) (Ratliff '98). For a 45 kg subject the MTD of an L-AMT single weekly dose is 5.85 mg. Hence 3.0 mg LD-AMT (1.5 mg/wk L-AMT), the maximum dose in this study, is for all subjects approximately 4-fold below the MTD. Mucositis and stomatitis were the dose-limiting toxicity and the earliest and most sensitive indicator of toxicity. Other common toxic manifestations, at or just beyond the MTD, included GI disturbances, abdominal cramps, diarrhea, hemorrhage, leukopenia, skin changes and alopecia. In our phase 1 and 2 oncology studies weekly L-AMT was used to safely treat over 100 adult and pediatric subjects, including 20 subjects who were treated for over two years (Ratliff '98; Cole '05; Cole '07).

In addition, in our 2010 bioequivalence study in subjects with psoriasis (AMT-PSO-101) LD-AMT was shown to be bioequivalent to L-AMT. These results are further supported by our trial (AMT-RA-202) in adult subjects with rheumatoid arthritis that has demonstrated the safety of a dose of 3.0 mg LD-AMT, without folic acid supplementation, for 12 weeks. It is expected that the 3.0 mg LD-AMT to be used in this clinical trial will not cause detectable toxicities.

Finally, AMT is known to cause congenital malformations in animals and humans (Thiersch '50; Warkany '59; Shaw '68). As a result, AMT is handled as an FDA Pregnancy Category X agent, requiring effective birth control during treatment and for 90 days after the cessation of treatment. If an oral hormonal birth control is used, then it should be in use at least 30 days prior to the first study

treatment. The agent is not used in patients who are pregnant, or until pregnancy can be ruled out in women of child-bearing potential.

3 OVERVIEW OF INVESTIGATIONAL PLAN

3.1 Study Design

This is a phase 2, multi-center, randomized, double-blind, placebo-controlled, clinical trial to investigate the efficacy, safety, of LD-AMT in the treatment of subjects with moderate-to-severe psoriasis. Folate metabolism biomarkers will be study to determine their correlation with efficacy and safety. Forty-six subjects will be randomized to one of two parallel treatment arms: LD-AMT (3 mg) or placebo, in a 1:1 ratio. LD-AMT tablets (overencapsulated) or placebo (overencapsulated) will be administered once weekly for 14 weeks. Randomized subjects will initially enter a 14-week treatment phase, followed by a 6-week post-treatment phase. The first study drug administration will be on Day 0.

Subjects in both treatment groups will receive 14 once weekly oral treatments.

Group	Treatment Assignment	Route	Schedule	N=46
1	3.0 mg AMT	oral	Once weekly x 14	23
2	placebo	oral	Once weekly x 14	23

General safety will be evaluated for each subject on Days 0, 14, 42, 70, 98, 119, and 140. Subjects will be evaluated for signs and symptoms of study drug intolerance. Subjects will complete weekly diaries to record study drug administration, and signs and symptoms of AEs. Blood will be obtained at screening and on Days 0, 14, 42, 70, and 98.

3.2 Primary and Secondary Endpoints

3.2.1 Co-Primary Efficacy Endpoints

The co-primary endpoints are:

- The proportion of subjects achieving Psoriasis Area and Severity Index of 75% (PASI 75) at study Day 98 (14 weeks).
- Static Physician Global Assessment (sPGA) dichotomized to success or failure at study Day 98 (14 weeks).

3.2.2 Secondary Efficacy Endpoints

- Proportion of subjects achieving PASI 50 at study Day 98 (14 weeks).
- Mean reduction in the PASI at study Day 98 (14 weeks).
- Proportion of subjects achieving “success” in erythema at study Day 98 (14 weeks).

- Proportion of subjects achieving "success" in scaling at study Day 98 (14 weeks).

- Proportion of subjects achieving "success" in plaque induration at study Day 98 (14 weeks).

3.2.3 Primary Safety Endpoints

Any abnormal laboratory values, abnormal vital signs, reported symptoms, or physical examination findings will be documented by the Investigator as adverse events. The safety assessments will be based on all reported adverse events, and changes in laboratory values from baseline. The severity and relationship to treatment will be recorded for all adverse events. Adverse events will be coded for summary and analysis using standardized preferred terms and system organ class.

3.2.4 Exploratory Endpoints

- Mean hematologic (e.g., hemoglobin, platelets, leukocytes) and hepatic laboratory (e.g., SGOT, SGPT) values over the treatment-phase

- Folate Metabolism: The evaluation will be based on the comparative analysis of mitochondrial localizing and cytoplasmic localizing folate metabolism enzymes by analysis of gene expression levels determined by RNA sequencing, e.g., DHFRL1 (mitochondrial) and DHFR (cytoplasmic). These analyses will be performed on subject RNA isolated from whole blood obtained at baseline.

3.3 Study Sites

This trial will be conducted at two study sites (Menter Dermatology Research Institute (MDRI), Dallas, TX, and Dermatology Associates (DAS), Seattle, WA). All study products will be stored at each site under controlled conditions.

3.4 Number of Subjects

At the end of this trial, if safety concerns have not been observed, a total of 46 subjects will have been enrolled (i.e., will have received at least one study drug dose). Of these, 23 will have received oral LD-AMT 3.0 mg, and 23 will have received oral placebo. It is anticipated that approximately 50 subjects will be screened to enroll the 46 subjects into the study.

3.5 Estimated Duration/Completion of the Study

Each subject will be on study for 140 days (20 weeks). It will take approximately 18 months from enrollment of the first subject to complete the study. Completion of the Day 140 assessment for the last enrolled subject is estimated to occur 18 months after initial enrollment.

3.6 Randomization

The principal investigator (or qualified designees) will be responsible for all study drug accounting and distribution. A randomization list will be generated by the Syntrix Pharmaceutical Division in blocks of appropriate size resulting in a treatment ratio of 1:1 for 3.0 mg LD-AMT and placebo. The randomization list will indicate treatment (3.0 mg LD-AMT or placebo) by consecutive Participant ID number (PID#) (a unique three-digit PID#). The randomization list will remain under control of the Syntrix Pharmaceutical Division. The Syntrix Pharmaceutical Division will ship participant study drug kits to the study sites. Each participant's study drug kit will be composed of a bottle containing 14 study drug doses (14 capsules), and each bottle will be labeled with a PID# that corresponds to the study drug treatment assigned by the randomization list. The label will not indicate the treatment. Study drug kits will be assigned to participants by sequentially increasing PID# as indicated on the bottle label. The PID# on the study drug kit assigned to a participant becomes the participant's assigned PID#. The assigned PID# will be recorded in the Screening Log with the corresponding participant. Each subject PID# will be given a site-specific two-digit prefix that identifies the site (01 = MDRI; 02 = DAS).

All subjects who sign consent and who meet all inclusion/exclusion criteria are eligible to receive study drug. When eligible subjects present for the Day 0 (baseline) visit, they are assigned a study drug kit. Study drug kits are assigned to participants by sequentially increasing PID# as indicated on the bottle label. The PID# on the study drug kit assigned to a participant becomes the participant's assigned PID#.

A total of 46 subjects will be randomized into this study. The randomization list will be generated by the Syntrix Pharmaceutical Division such that subjects will be randomly assigned in blocks of appropriate size resulting in a 1:1 ratio of subjects assigned to LD-AMT 3.0 mg once per week or placebo once per week. The randomization list will indicate treatment assignment and corresponding PID #.

Once a subject is found to be eligible and has completed the baseline assessments, they will be considered enrolled in the study. At study Day 0 they will be randomized to treatment assignment and will be provided with masked study drug.

The Syntrix Pharmaceutical Division will keep the randomization lists in a secure location. If the Investigators request unblinding of a participant's treatment assignment, provided it is not a life-threatening event, the Investigator will provide the NIAID and Syntrix MMs with sufficient information to decide if unblinding should occur. If the event is life threatening and the MMs are not immediately available to review the request, the investigator can contact the Syntrix Medical Monitor and that subject's treatment assignment will be revealed by the Syntrix Pharmaceutical Division to the Syntrix Medical Monitor. All unblinding of participants will be reported to the MMs, the ISM, SCG, the study statistician by the close of the next business day. It is expected that given the stopping algorithms and availability of the antidote leucovorin, treatment assignments will not need to be unmasked to adequately respond to possible drug-related toxicities.

Syntrix Pharmaceutical Division will not release participant treatment assignments to anyone during the study, except as may be required for safety. The final unmasking of all subject

assignments may only be made at the direction of the Sponsor. This is planned to occur after all subjects have completed the study and the study database has been locked.

3.7 Administration of Study Drug

Study drug administration is scheduled for the first Day of each Study Week (Day 0, Day 7, Day 14, etc.). All efforts should be made to maintain an exact weekly administration cycle of study drug. Accuracy to within 12 hours should be sought by the Investigator and the subject. If the exact weekly administration of study drug is missed, then study drug should be administered as soon as possible within two days (e.g., the weekly study drug administration is on Wednesday and is missed, then the study drug should be administered as soon as possible on Thursday or Friday). If the study drug administration is missed for more than two days, then that week's administration should be skipped, and study drug administration should resume on the next weekly cycle day. This is to avoid a temporal spacing of dosings that might precipitate toxicity (i.e., < 4 day interval between doses). Actual dates of all study drug administration should be noted in the CRFs. All subsequent study drug administrations should proceed according to the ideal weekly cycle referenced back to the date of randomization (Study Day 0), and should not be adjusted to the deviated study drug administration date. At each study visit, subjects will be given diaries to record study drug administration dates.

3.8 Identification of Source Data Recorded Directly on the CRF

All data entered in the CRFs must have a valid source document, either written or electronic. Data may not be recorded directly in the CRF without a source document unless specified in study specific procedures.

4 STUDY POPULATION

4.1 Inclusion Criteria

1. Be 18 years of age or older.

2. Have a diagnosis of moderate-to-severe psoriasis for at least 6 months confirmed by a dermatologist, defined here as plaque-type psoriasis affecting a body surface area of $\geq$10% and a PASI of $\geq$10.

3. Agree to avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet light sources during the study.

4. Ability to understand and sign written informed consent.

5. Heterosexually active men and women of childbearing potential must use two methods of contraception during the study (20 weeks) and for 90 days after study completion. The two methods of birth control may be used simultaneously in the same subject or simultaneously in both partners. The two birth control methods can be (a) 2 barrier methods or (b) a barrier method plus a hormonal method to prevent pregnancy.

Barrier methods include: condom (female or male), copper intrauterine device, sponge, or spermicide.

If an oral hormonal birth control is being used, then it should be in use at least 30 days prior to the first study drug administration. Hormonal Methods include: any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent, including oral, subcutaneous, intrauterine, or intramuscular agents.

6. For pre-menopausal women, a negative pregnancy test, obtained at screening visit and at study visits Week 0, Week 6, Week10, Week 14, and Week 20. If at any visit during the Treatment Phase (see Appendix A) a positive pregnancy test is returned, the subject will be discontinued from any further study drug.

7. Negative serology for HIV1/2, hepatitis B and hepatitis C.

8. The following screening laboratory blood tests must have the following values, or not clinically significant as determined by the PI and Medical Monitor: WBC WNL; absolute neutrophil count > lower limit of normal; platelet count WNL; hemoglobin >10.0 g/dL; AST < 2.5 x the upper limit of normal.

9. Adequate renal function: Creatinine clearance estimated by Cockcroft-Gault formula >60 ml/min

4.2 Exclusion Criteria

Subjects who meet ANY of the following criteria will be excluded from the study (ineligible):

1. Known history of hepatitis, HIV infection, interstitial lung disease.

2. Greater than moderate alcohol consumption on a regular basis (moderate consumption for females is 1 drink or 1 glass of wine a day; for males is 2 drinks or 2 glasses of wine a day) and unwilling, or unable, to control consumption during the study period.

3. Prior use of AMT.

5. Use of these biologic treatments in the timeframes specified:

- Within 9 months of first study drug dose: ustekinumab (Stelara).
- Within 12 weeks of first study drug dose: any experimental therapy for psoriasis or rheumatoid arthritis.
- Within 8 weeks of first study drug dose: infliximab (Remicade), adalimumab (Humira).
- Within 4 weeks of first study drug dose: etanercept (Enbrel).

- Other biologic therapies will have discontinuation periods determined by 5x their half-life.

6. Within 90 days prior to Day 0 and at any time while on study, the use of MTX.

7. Within 4 weeks prior to randomization and at any time while on study, use of phototherapy (e.g., UVB, narrow band UVB, Goeckerman regimen, Ingram regimen, PUVA), systemic medications (e.g. acitretin, mycophenolate mofetil, tacrolimus/FK506, cyclosporine A, azathioprine, 6-thiogaunine, sulfasalazine, hydroyurea, calcitriol, apremilast, any systemic immunosuppressants), lithium, or any treatments that could affect psoriasis or sPGA evaluations. Subjects are eligible 4 weeks after the last dose of any of the aforementioned treatments was received.

8. Within 2 weeks prior to randomization and at any time while on study, use of any topical medications or treatments that could affect psoriasis evaluations (e.g., corticosteroids, anthralin, vitamin D3/calcitriol and analogues such calcipotriene and tacalcitol, synthetic retinoids such as tazarotene, coal tar, and keratolytics such as salicylic acid, lactic acid and urea including those contained in over-the-counter medicated shampoos). Subjects are eligible 2 weeks after the last dose of any of the aforementioned treatments was received.

   Note: Over-the-counter topical steroids will be permitted for use limited to the face, axilla, and/or genitalia, as needed. These topical medications should not be used within approximately 24 hours prior to study visits Day 0 and Day 98. Over-the-counter shampoos for the treatment of psoriasis of the scalp are also permitted.

9. Use of emollients on the morning of the first (Week 0) study visit.

10. Within 2 weeks prior to Study Day 0, or on Study Day 0, or at any time during the study, use of any of the following medications that may result in drug/drug interactions with AMT: trimethoprim with or without sulfamethoxazole; sulfonamides; sulfonylureas; pyrimethamine; triamethamine; salicylates; non-steroidal anti-inflammatory (NSAID) drugs including ibuprofen; dipyridamole; colchicine; probenecid; aminoglycosides; theophylline; phenytoin; and folinic acid (i.e., leucovorin).

11. Known concurrent malignancy except basal or squamous cell skin carcinoma, or cervical carcinoma in situ.

12. Concurrent participation in another clinical trial involving experimental treatment within 30 days of Study Day 0.

13. Current and uncontrolled infection, cardiovascular, renal, pulmonary, hepatic or GI conditions that will interfere with the conduct of the trial or pose a morbid risk.

14. Investigator's opinion that a concurrent disease or condition impairs the subject's ability to complete the trial: includes psychological, familial, sociological, geographical or medical conditions.

15. Breast-feeding.

4.3 Discontinuation of Study Drug

Subjects with any of the following conditions will be discontinued from additional study drug:

- Pregnancy
- Adverse events or concomitant medication that in the opinion of the Principal Investigator (or designated sub-investigator) would preclude further drug
- Dose limiting toxicity
- Malignancy

All subjects who have study drug discontinued will be followed until resolution or stabilization of the event and will remain on study for follow-up visits and safety evaluations.

4.4 Subject Withdrawal from the Study

Subjects will be free to withdraw from the study at any time, for any reason, and without prejudice to further treatment. Any subject who withdraws from the study, regardless of reason, will not be allowed to re-enroll in this study. Reasons for withdrawal will be recorded on the appropriate CRF. The final report will include reasons, if available, for withdrawal and any necessary treatment.

Anytime a subject withdraws from the study, for whatever reason, including voluntary withdrawal, every attempt should be made to evaluate all procedures planned for the Study Day 98 visit.

4.5 Subject Replacement

Subjects will not be replaced.

5 STUDY PROCEDURES

A summary of study procedures is provided in Appendix A.

5.1 Consent and Screening Procedures

Screening evaluations will occur during the 30-day period prior to Day 0 (i.e., Day -30 to Day -1). More than one clinic visit may be required in order to complete all screening evaluations for a subject. Screening labs may be repeated if necessary for parameters with out of range results (e.g., a subject with low hemoglobin may be tested again within 14 days or more after the initial test, as long as it is within the 30-day window). The purpose of the screening period is to assure that the

subjects meet the study entry criteria and that they adequately comprehend the protocol and its requirements.

Prior to the start of screening, the investigator (or study personnel) obtains a signed study consent form from each potential study participant. The Screening procedure includes the following assessments:

1. Explain the study and screening procedures to the subject.

2. Review the informed consent form with the subject and obtain his/her signature and date of signature on the informed consent document. Provide the subject with a copy of the signed consent form.

3. Assign the subject a screening identification number (SID#). This number will be assigned sequentially and must be recorded on the sites screening log. The first two digits of the SID# identify the site (e.g., 01 = Clinic X). The next three digits identify the subject. For example, the first subject screened, if at the center designated "01", will be assigned the SID# 01-001, the second subject if at the same site, 01-002. If a subject is re-screened they will be assigned a new SID#.

4. Document medical history including smoking history, chronic obstructive pulmonary disease, sleep apnea, and drug and alcohol consumption. Rule out any allergies, acute or chronic illness that could interfere with study evaluations, cancer or treatment for cancer within 3 years, participation in experimental protocols within past 30 days, psychiatric illness, alcohol or drug abuse.

5. Record any signs and symptoms the subject is experiencing at the screening visit on the appropriate baseline source document and CRF.

6. Record any current use of medications, including any taken within the past 6 weeks. Concomitant medications will include contraception that is being used during the trial.

7. Assess vital signs: blood pressure, heart rate and temperature.

8. Assess psoriasis body surface area involvement and PASI.

9. Perform physical examination. Measure weight and height of the subject. BSA can be calculated. Rule out tattoos or any other dermatological condition that could adversely affect the psoriasis evaluations.

10. Obtain a urine specimen for urinalysis.

11. If subject is female of child-bearing potential, perform a urine pregnancy test (beta-HCG).

12. Collect approximately 15 ml blood as follows:

    - 5 mL anti-coagulated whole blood for CBC, white cell differential and platelet count.

- 5 mL whole blood for serum chemistry testing. Chemistries to include: BUN, creatinine, ALT, AST, total bilirubin, alkaline phosphatase, albumin, and total protein.

- 5 mL whole blood for serology testing. Serology tests to include: HIV1/2, hepatitis B surface antigen (HBsAg), and hepatitis C antibody (HCV AB).

13. Obtain a chest X-ray (CXR) (a CXR within the previous 6 months (to date of screening visit) may be used instead of performing a new CXR).

14. Review CXR and lab results. Lab results must meet the listed inclusion criteria. If they do not, then the subject is ineligible.

15. If subject meets eligibility criteria, then:

    - Schedule Study Day 0 visit. When scheduling this Week 0 visit, be sure to inform subjects not to eat for at least 1 hour before their visit as that visit will be one where study drug is given.

    - Review subject randomization procedure. Notify central randomization or appropriate sponsor designee of new subject to be randomized.

16. Complete all CRFs for the visit.

5.2 Week 0 - Day 0 (Baseline) Evaluations

Subjects who meet all screening evaluation criteria will be asked to return to the clinic for the baseline visit. The clinical site coordinator or designee will confirm that appropriate study drug is available. As the subject is randomized and assigned to a study drug treatment, the study drug bottle label PID# will be recorded on appropriate CRFs and logs as required. The PID# will be composed of the two-digit site number, e.g., 01=Clinic X, followed by the subject-specific three-digit number that links the study drug provided to the masked study drug treatment assigned, e.g., 01-101. This PID# must be recorded and linked to the corresponding SID# in the screening log.

Upon arrival, the following evaluations will be completed:

1. Perform physical exam as directed by subject history.

2. Assess vital signs: blood pressure, heart rate, and temperature.

3. Review and record concomitant medications (including alternative and complementary treatments) and determine if they are within the prohibited drugs.

4. Verify that the subject is compliant with the contraception requirement.

5. If subject is a woman of child-bearing potential, then perform a urine pregnancy test (beta-HCG). A negative result must be confirmed before subject is randomized and study drug is administered.

6. Perform psoriasis assessments (PASI, sPGA, Dermatology Life Quality Index).

7. Collect 5 mL or less blood prior to study drug administration for folate metabolism evaluations. The blood sample will be processed as described in the study specific procedure manual.

8. Subjects who continue to meet entry criteria, who have completed baseline evaluations, and have provided signed informed consent will be provided their first dose of study drug.

9. Randomize subject to appropriate treatment assignment. Provide subject with the study drug.

10. Instruct subject they may eat 1.0 hr after the study drug administration. Clear liquids are permitted.

11. Record any adverse events that occur after study drug administration.

12. Instruct subject to not ingest solid food at least 1 hour before, and 1 hours after, the next study drug administration (clear liquids are okay).

13. Instruct subject on the completion of the study drug diary which will document the AMT doses for home administration. The diary will be used to capture the dosing of the AMT as well as to note any signs or symptoms that may occur in between the site visits. Provide the subject with sufficient blank diaries to last until their next clinic visit. Ask subject to bring their completed diary to their next clinic visit. The Diary shall be reviewed with the subject prior to leaving the study site; clear understanding of how to complete the diary shall be documented by the research staff, with contact information for the subject in the event that there are questions afterwards.

14. Remind subject to bring study drug bottle to next (and all) study clinic visits to enable study drug accounting.

15. The completed diary will be collected by the study site and retained in the subject source document binder on Day 14 and a new diary will be provided, to be collected at the next study visit.

16. Complete all CRFs for the visit.

5.3 Week 2 - Day 14 Evaluations (±2)

Upon arrival, the following evaluations will be completed:

1. Review subject diary and record:

- Concomitant medications (including alternative and complementary treatments) and determine if they are within the prohibited drugs.

- Adverse events.

- Study drug dosing compliance.

2. Verify that the subject is compliant with the contraception requirement.

3. Collect blood for CBC and chemistries. Results must be reviewed before administration of study drug on Day 21 so that appropriate study drug dose adjustments (Section 9.1) can be made.

4. If subject is a woman of child-bearing potential, then obtain a urine sample and perform a pregnancy test (beta-HCG). A negative result must be confirmed before additional study drug is administered.

5. If subject remains eligible study drug can be administered. Subject will be given sufficient study drug for home administration until subject returns to the clinic for the next scheduled visit in 4 weeks.

6. Record any adverse events that occur after study drug administration.

7. Instruct subject to not ingest solid food at least 1 hour before and 1 hour after study drug administration (clear liquids are okay).

8. Remind subject to bring study drug bottle to next (and all) study clinic visits to enable study drug accounting.

9. File the completed diaries in the subject source document binder and provide the subject with sufficient blank diaries to last until their next clinic visit.

10. Instruct subject on the completion of the study drug diary which will document the AMT doses for home administration. The diary will be used to capture the dosing of the AMT as well as to note any signs or symptoms that may occur in between the site visits. Ask the subject to bring their completed diary to their next clinic visit. The Diary shall be reviewed with the subject prior to leaving the study site; clear understanding of how to complete the diary shall be documented by the research staff, with contact information for the subject in the event that there are questions afterwards.

11. Instruct subject on home administration of study drug on Study Day 21, 28, and 35.

12. Complete all CRFs for the visit.

5.4 Week 6 - Day 42 Evaluations (±3)

Upon arrival, the following evaluations will be completed:

1. Review subject diary and record:

   - Concomitant medications (including alternative and complementary treatments) and determine if they are within the prohibited drugs.
   - Adverse events.
   - Study drug dosing compliance.

2. Verify that the subject is compliant with the contraception requirement.

3. If subject is a woman of child-bearing potential, then obtain a urine sample and perform a pregnancy test (beta-HCG). A negative result must be confirmed before additional study drug is administered.

4. Perform physical exam as directed by subject history.

5. Collect blood for CBC and chemistries. Results must be reviewed before administration of study drug on Day 49 so that appropriate study drug dose adjustments (Section 9.1) can be made.

6. If subject remains eligible study drug can be administered. Subject will be given sufficient study drug for home administration until subject returns to the clinic for the next scheduled visit in 4 weeks.

7. Record any adverse events that occur after study drug administration.

8. Instruct subject to not ingest solid food at least 1 hour before and 1 hour after study drug administration (clear liquids are okay).

9. Remind subject to bring study drug bottle to next (and all) study clinic visits to enable study drug accounting.

10. File the completed diaries in the subject source document binder and provide the subject with sufficient blank diaries to last until their next clinic visit.

11. Instruct subject on the completion of the study drug diary which will document the AMT doses for home administration. The diary will be used to capture the dosing of the AMT as well as to note any signs or symptoms that may occur in between the site visits. Ask the subject to bring their completed diary to their next clinic visit. The Diary shall be reviewed with the subject prior to leaving the study site; clear understanding of how to complete the

diary shall be documented by the research staff, with contact information for the subject in the event that there are questions afterwards.

12. Instruct subject on home administration of study drug on Study Day 49, 56, and 63.

13. Complete all CRFs for the visit.

5.5 Week 10 - Day 70 Evaluations (±3)

Upon arrival, the following evaluations will be completed:

1. Review subject diary and record:

   - Concomitant medications (including alternative and complementary treatments) and determine if they are within the prohibited drugs.
   - Adverse events.
   - Study drug dosing compliance.

2. Verify that the subject is compliant with the contraception requirement.

3. If subject is a woman of child-bearing potential, then obtain a urine sample and perform a pregnancy test (beta-HCG). A negative result must be confirmed before additional study drug is administered.

4. Perform physical exam as directed by subject history.

5. Collect blood for CBC and chemistries. Results must be reviewed before administration of study drug on Day 77 so that appropriate study drug dose adjustments (Section 9.1) can be made.

6. If subject remains eligible study drug can be administered. Subject will be given sufficient study drug for home administration until subject returns to the clinic for the next scheduled visit in 4 weeks.

7. Record any adverse events that occur after study drug administration.

8. Instruct subject to not ingest solid food at least 1 hour before and 1 hour after study drug administration (clear liquids are okay).

9. Remind subject to bring study drug bottle to next (and all) study clinic visits to enable study drug accounting.

10. File the completed diaries in the subject source document binder and provide the subject with sufficient blank diaries to last until their next clinic visit.

11. Instruct subject on the completion of the study drug diary which will document the AMT doses for home administration. The diary will be used to capture the dosing of the AMT as well as to note any signs or symptoms that may occur in between the site visits. Ask the subject to bring their completed diary to their next clinic visit. The Diary shall be reviewed with the subject prior to leaving the study site; clear understanding of how to complete the diary shall be documented by the research staff, with contact information for the subject in the event that there are questions afterwards.

12. Instruct subject on home administration of study drug on Study Day 77, 84, and 91. Inform subject that this will be the last visit where they will be receiving drug. Subjects will need to bring back study drug bottle and all other study related materials at their next visit.

13. Complete all CRFs for the visit.

5.6 Week 14 - Day 98 Evaluations (±3)

Upon arrival, the following evaluations will be completed:

1. Review subject diary and record:

   - Concomitant medications (including alternative and complementary treatments) and determine if they are within the prohibited drugs.
   - Adverse events.
   - Study drug dosing compliance.

2. Verify that the subject is compliant with the contraception requirement. Remind subject to refrain from donating sperm as well as to continue their birth control methods for the next 90 days (3 months).

3. If subject is a woman of child-bearing potential, then obtain a urine sample and perform a pregnancy test (beta-HCG).

4. Perform physical exam as directed by subject history.

5. Assess vital signs: blood pressure, heart rate and temperature.

6. Collect blood for CBC and chemistries.

7. Obtain a urine specimen for urinalysis.

8. Perform psoriasis assessments (PASI, sPGA, Dermatology Life Quality Index).

9. File the completed diaries in the subject source document binder and provide the subject with sufficient blank diaries to last until their next clinic visit.

10. Instruct the subject on the completion of the diary which will be used to capture any signs or symptoms that may occur in between the site visits. Ask subject to bring their completed diary to their next clinic visit. The Diary shall be reviewed with the subject prior to leaving the study site; clear understanding of how to complete the diary shall be documented by the research staff, with contact information for the subject in the event that there are questions afterwards.

11. Complete all CRFs for the visit.

5.7 Week 17 - Day 119 Evaluations (±4)

The following evaluations will be performed by telephone:

1. Review subject diary and record:

    - Concomitant medications (including alternative and complementary treatments) and determine if they are within the prohibited drugs.

    - Adverse events.

2. File the completed diaries in the subject source document binder and provide the subject with sufficient blank diaries to last until their next clinic visit. Instruct the subject on the completion of the diary which will be used to capture any signs or symptoms that may occur in between the site visits. Ask subject to bring their completed diary to their next clinic visit. The Diary shall be reviewed with the subject prior to leaving the study site; clear understanding of how to complete the diary shall be documented by the research staff, with contact information for the subject in the event that there are questions afterwards.

3. Verify that the subject is compliant with the contraception requirement.

4. Complete all CRFs for the visit.

5.8 Week 20 - Day 140 Evaluations (±4)

Upon arrival the following evaluations will be completed:

1. Review subject diary (file the completed diaries in the subject source document binder) and record:

    - Concomitant medications (including alternative and complementary treatments) and determine if they are within the prohibited drugs.

    - Adverse events.

2. Verify that the subject is compliant with the contraception requirement.

3. If subject is a woman of child-bearing potential, then obtain a urine sample and perform a pregnancy test (beta-HCG).

4. Complete all CRFs for the visit.

5.9 Concomitant Medications

Subjects may use concomitant medications as permitted by the protocol. All medications and immunizations, prescription or non-prescription (including over the counter, alternative, and traditional preparations), including any medication used in the treatment of an AE, taken at any time from the day of screening evaluation, through the end of post drug surveillance, must be recorded on the Concomitant Medication CRF.

Over-the-counter topical steroids will be permitted for use limited to the face, axilla, and/or genitalia, as needed. These topical medications should not be used within approximately 24 hours prior to study visits Day 0 and Day 98. Over-the-counter shampoos for the treatment of psoriasis of the scalp are also permitted.

5.10 Prohibited Medications and Procedures

1. At any time while on study, use of phototherapy (e.g., UVB, narrow band UVB, Goeckerman regimen, Ingram regimen, PUVA), systemic medications (e.g., MTX, cyclosporine, biologic therapies, interleukin-2-diptheria-toxin, acitretin, mycophenolate mofetil, tacrolimus/FK506, azathioprine, 6-thiogaunine, sulfasalazine, hydroyurea, calcitriol, apremilast, any systemic immunosuppressants), lithium, or any treatments that could affect psoriasis evaluations are prohibited.

2. At any time while on study, any topical medications or treatments that could affect psoriasis evaluations (e.g. corticosteroids, anthralin, vitamin D3/calcitriol and analogues such calcipotriene and tacalcitol, synthetic retinoids such as tazarotene, coal tar, and keratolytics such as salicylic acid, lactic acid and urea including those contained in over-the-counter medicated shampoos) are prohibited. Subjects are eligible 2 weeks after the last dose of any of the aforementioned treatments was received.

3. Within 2 weeks prior to Study Day 0, or on Study Day 0, or at any time during the study, use of any of the following medications that may result in drug/drug interactions with AMT: trimethoprim with or without sulfamethoxazole; sulfonamides; sulfonylureas; pyrimethamine; triamethamine; salicylates; non-steroidal anti-inflammatory (NSAID) drugs including ibuprofen; dipyridamole; colchicine; probenecid; aminoglycosides; theophylline; phenytoin; and folinic acid (i.e., leucovorin) unless prescribed by the investigator to treat study drug related toxicity.

4. At any time while on study elective surgical procedures are prohibited.

5.11 Contraception Requirements for Men and Women

Aminopterin is embryo-toxic and teratogenic in animals (Bellairs '54; Johnson '64) and humans (Thiersch '50; Meltzer '56; Warkany '59; Shaw '68), and is reported to have transient effects on human sperm. Men and non-pregnant, nonbreast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized (e.g., vasectomy, hysterectomy, tubal ligation), or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 2 years), or 3) amenorrheic for <2 years without a hysterectomy and oophorectomy and with a documented FSH value in the postmenopausal range, or 4) not heterosexually active for the duration of the study, or 5) heterosexually active and willing to use two methods of birth control throughout the study starting with Day 0 through 90 days after the last dose of study medication. The 2 methods of birth control may be used simultaneously in the same subject or simultaneously in both partners.

The two birth control methods can be (a) 2 barrier methods or (b) a barrier method plus a hormonal method to prevent pregnancy.

Barrier Methods. The following are adequate barrier methods of contraception: diaphragm, condom (female or male), copper intrauterine device, sponge, or spermicide.

Hormonal Methods. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent, including oral, subcutaneous, intrauterine, or intramuscular agents. If an oral hormonal birth control is used, then it should be in use at least 30 days prior to the first study treatment. The agent is not used in patients who are pregnant, or until pregnancy can be ruled out in women of child-bearing potential.

5.12 Unscheduled Visits

If the subject attends the clinic for an unscheduled visit, all information must be recorded in the source document, AEs must be reported on the AE form, and the history, physical exam, procedures, treatments, interventions, or outcomes will be reported on the appropriate unscheduled visit CRF.

5.13 Missed Visits

Any missed study-specified visit will be documented on the appropriate CRF.

5.14 Subject Samples

Folate metabolism samples will not be used for additional analyses without subject consent. If not used within 10 years from the time of the study's last subject clinic visit, the samples will be destroyed by the Sponsor.

6 Evaluations of Folate Metabolism

Analysis of the role of the cytoplasmic and mitochondrial compartments in folate metabolism will be performed. Assessment of folate metabolism will be performed with blood specimens

obtained at baseline. Endpoints of interest include the ratio of mitochondrial to cytoplasmic gene expression levels of DHFR and thymidylate synthase. These results will be correlated with study trial efficacy and safety outcomes.

7 STUDY DRUG

7.1 Study Drug Supplies and Handling

Syntrix or CRO designee will supply identical appearing capsules containing placebo or 3 mg LD-AMT. The capsules will be supplied in a coded bottle. The Sponsor designee will maintain the blinded treatment assignment list and will send coded study drug bottles to the clinical sites for each subject. The clinical investigator or designee will provide subjects with sufficient study drug at the clinic visits. The Study drug will be shipped under controlled conditions. A second bottle can be used by the subjects to take home sufficient study drug for the weekly doses to be administered at home in between clinic visits.

7.2 Labeling

Study drug will be distributed in bottles with labels that indicate that they contain study drug, and with the caution statement "Caution: New Drug – Limited by United States Law to Investigational Use."

7.3 Storage

Study drug will be stored at 15-30°C, protected from light. The supplies will be accessible to authorized personnel only.

7.4 Preparation, Administration, and Dosage of Study Drug

Study drug or matching placebo will be provided to the site; the treatment period is 1 capsule weekly, a total dose of 14 capsules. An additional bottle can be used by the subjects to take home sufficient study drug for the weekly doses to be administered at home in between clinic visits. During the clinic visits at Week 0, 2, 6, and 10, the study drug can be taken by the subject in the clinic after all study procedures have been completed for that visit.

Study subjects will be instructed to take their study drug on a designated day each week in between the clinic visits; they will be instructed that this drug schedule is to be kept unless otherwise instructed by the research staff. If the dosing schedule is changed or altered in any way for any reason, the subject will be asked to discuss this with the investigative team at the clinic.

7.5 Accountability of Study Agent

7.5.1 Receipt of Study Agent

As soon as the clinical team member receives study drug from Syntrix or designee, the accuracy of the clinical supply shipping form will be verified and the appropriate shipment accounting form

must be completed and returned to Syntrix or its designee. The clinical team member should retain a copy of this form for the Investigator's file.

7.5.2 Record of Administration and Dispensing

Accurate recording of all administration and dispensing of study drug will be made on the appropriate logs and CRFs. All used containers, study drug not dispensed, and accountability records must be retained for eventual accountability by the Sponsor or designee.

7.5.3 Unused Study Drug

At the end of the study the Investigator or designee will be responsible for retaining investigational supplies at the sites pending instructions from Syntrix or designee for returning all unused study drug to Syntrix or designee as instructed. Following final accounting, as instructed by Syntrix or designee, used canisters will be discarded according to hospital or clinic policy or returned to Syntrix or designee.

8 ADVERSE EVENTS

8.1 Specification of Safety Parameters

The safety assessments will be based on clinical AEs reported by the subject or observed by the investigator (or appropriate designee) and laboratory AEs reported as test results. AEs will be recorded on the AE CRF. Clinical AE relationship to study drug will be determined by the investigator (or appropriate designee) and recorded on the AE CRF. Laboratory AE relationship to study drug will be determined or recorded on the AE CRFs. Laboratory AEs considered not clinically significant will ***not*** be recorded on the AE CRF.

8.2 Definitions

8.2.1 Adverse Event

An AE is any untoward medical occurrence in a subject administered the study drug that does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not related to the study drug.

8.2.2 Serious Adverse Event

A Serious Adverse Event is defined as an AE occurring while subject is on study resulting in one of the following conditions:

- Death,
- Life Threatening* (defined as a subject at immediate risk of death at the time of the event),
- Inpatient hospitalization or prolongation of existing hospitalization,
- Congenital anomaly or birth defect,

- A persistent or significant disability/incapacity.

*Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a SAE when, based upon medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. 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.

8.2.3 Unexpected Adverse Event

Unexpected AEs are those not described in the Investigator's Brochure. Expected AEs are those described in the IB. Expected treatment related AEs include, but are not limited to, grade 1-2: stomatitis, mucositis, nausea, vomiting, gastrointestinal cramping, anemia, leukopenia, thrombocytopenia and elevations in liver transaminases. The IB should be consulted for a comprehensive listing. The duration of such AEs will typically be less than 1 week.

8.3 Assessment of Adverse Events

Assessment of clinical AE/SAE must be by the Investigator or appropriate designee, and should include the intensity (severity) of the event and the relationship to study drug.

8.3.1 Severity Grading

The NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4.0) will be used to categorize AEs and SAEs and to score severity (online at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

8.3.2 Relationship of Adverse Event to Study Drug

Clinical AE/SAEs must have their relationship to study drug assessed using the following terms (NOTE: relationship is not a factor in determining what is or is not reported in the study):

- Definitely Related (5)

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 drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- Probably Related (4)

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

sequence to administration of the drug, 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.

- Possibly Related (3)

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, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably" or "definitely" as appropriate.

- Unlikely (2)

A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

- Not related (1)

The AE is completely independent of study drug administration, or evidence exists that the event is definitely related to another etiology. The alternative, definitive etiology must be documented.

Adverse events that are related to psoriasis or common syndromes will be considered related to the underlying disease and not to the study agent.

8.4 Diaries (Memory Aids)

Diaries will be distributed to subjects to aid in documentation of study drug administration, and to aid in collection of signs and symptoms of AEs. Subjects will be instructed to record the date or day of study drug administration. Subjects will also be instructed to record signs and symptoms of AEs.

8.5 Reporting Adverse Events

All AEs, regardless of severity or presumed relationship to study drug, will be documented on the AE CRF. All SAEs, and grade 3 and grade 4 hematologic AEs, and grade 4 hepatic AEs must be reported by the Principal Investigator (or designee) directly to Syntrix Pharmacovigilance within 24 hours by email or telephone. The reporting sequence for all SAEs, grade 3 and grade 4 hematologic AEs, and grade 4 hepatic AEs will be as follows:

1. The Principal Investigator (or designee) must report the event immediately (within 24 hours) to Syntrix Pharmacovigilance.

2. Syntrix Pharmacovigilance will then complete and forward an incident report by e-mail, containing all relevant information about the subject to the Syntrix MM, NIAID MM, and ISM within 48 hours of receipt of the report of the event.

3. The Syntrix MM must provide a written report by e-mail to Syntrix Pharmacovigilance, the NIAID MM, and the ISM within 2 working days of receipt of the initial incident report. This report must provide a recommendation as to whether the individual subject may continue to receive study drug (if more study drug is scheduled).

4. Syntrix Pharmacovigilance will forward the Syntrix and NIAID MM's written report and recommendation by e-mail to the Principal Investigator within 2 working days of receipt.

The Principal Investigator will meet his IRB reporting requirements.

All SAEs, grade 3 and grade 4 hematologic AEs, and grade 4 hepatic AEs (increased ALT, AST, alkaline phosphatase, total bilirubin) judged to be probably or definitely related to study drug will be reported by Syntrix to the FDA within 15 days of receipt of the report of the event.

8.6 Follow-up of Subjects with Adverse Events

All AEs must be followed to resolution or stabilization of the event.

8.7 Reporting of Pregnancy

Pregnant women are not eligible to participate in the study. Women are counseled regarding prevention of pregnancy and are required to avoid pregnancy during study participation by adhering to the contraception requirements of the study. If a subject becomes pregnant, no further doses of study drug will be given. The blind will be broken for this subject only, and the event recorded as a protocol deviation. The investigator should be informed immediately of any pregnancy in a participant or pregnancy of a female partner of a male participant occurring from randomization through 30 days after the participant completes the trial. Events surrounding the pregnancy should be recorded and reported to Syntrix following the instructions provided in the Sponsors Pharmacovigilance Instructions.

If there are complications during the pregnancy, the complications will be recorded as AEs in the usual way. The subject will be asked to report the outcome of the pregnancy. If there is a congenital anomaly in the infant, this will be recorded and reported as a SAE for the mother (i.e., the study subject).

8.8 Oversight of Data and Safety

As described in the study DSMP the Syntrix Clinical Group (SCG) in collaboration with NIAID medical officers will monitor AMT-PSO-201 ensure the safety of the subjects and the integrity of the data. Stuart Kahn, M.D., Medical Director of Syntrix will act as the Sponsors Medical Monitor.

Dr. Kahn will work closely with the NIAID Medical Monitor. Study accrual and Patient Status reports generated by the SCG that include delinquency, adverse event summaries, and a listing of enrollees will be provided to the MMs and the ISM.

9 ASSESSMENT OF RISK

9.1 Modification of Study Drug for a Subject

The NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4.0) will be used to score severity grade (online at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf or this protocol Appendix C)

9.1.1 Hematologic Adverse Events (Leukopenia, Thrombocytopenia, Anemia)

For grade 2 leukopenia, grade 2 thrombocytopenia, and grade 3 anemia: study drug is held for a maximum of 3 weeks. Monitoring is performed weekly until the grade 2 leukopenia, grade 2 thrombocytopenia, or grade 3 anemia AE resolves. Then study drug is resumed and the normal monitoring schedule is resumed. If grade 2 leukopenia, grade 2 thrombocytopenia, or grade 3 anemia continues for > 3 weeks, study drug is withdrawn permanently and leucovorin treatment considered.

For grades 3 and 4 leukopenia and thrombocytopenia, and grade 4 anemia: study drug is withdrawn permanently. Hematologic labs are retested until normal. Leucovorin treatment is considered for grade 3, and administered for grade 4 AEs

Hematologic AE Algorithm

Grade	Monitoring Schedule	Study Drug Dosing	Leucovorin Treatment *
2 **	Weekly until AE improves	Hold until AE improves (3 weeks maximum).	Consider for AEs > 3 weeks
3***	PI judgment until AE improves.	Permanent hold.	Consider
4	PI judgment until AE improves.	Permanent hold.	Yes

* 10 mg tablet orally once daily
** Excluding grade 2 anemia
*** Excluding grade 3 anemia

9.1.2 Hepatic Adverse Events

As recommended by the ACR for MTX monitoring, only AST (SGOT) is used to guide study drug dose modifications for hepatoxicity, unless other blood tests are grade 3 or 4.

If a subject experiences three grade 3 AST AEs then study drug is permanently withdrawn and weekly evaluations performed until the AE resolves. Leucovorin rescue is considered.

If a subject experiences a grade 4 AE, then study drug is permanently withdrawn and weekly evaluations performed until AE resolves. Leucovorin treatment is considered.

For grade 4 changes in ALT, alkaline phosphatase, total bilirubin and albumin, study drug is permanently held and the subject monitored weekly until the AE resolves.

Hepatic AE Algorithm

Grade	Monitoring Schedule	Study Drug Dosing	Leucovorin Treatment *
1	No change.	No change	No
2	No change	No change	No
3	Weekly until AE becomes grade 2, (then resume regular schedule).	After three grade 3 AEs, then study drug is withdrawn.	Consider
4	Change to weekly until AE resolves.	Study drug is withdrawn.	Consider

* 10 mg tablet orally once daily

9.1.3 Mucositis/Stomatitis Adverse Events

For oral mucositis grade 1 a dose suspension is not required. For mucositis grade 2 that persists for ≥ 3 weeks, study drug is held. For grade 3 or grade 4 mucositis study drug is held until grade 2 or lower are observed, and then study drug is resumed and the subject is re-examined in a week. If after two weeks lesions have not improved to grade 1, then study drug is withdrawn permanently. For persistent lesions of grade 2, or lesions > grade 2, leucovorin treatment (10 mg tablet orally once daily) can be given.

9.2 Criteria for Interrupting the Trial Based on Dose-Limiting Toxicity (DLT)

9.2.1 Rules for Discontinuing Study Drug in an Individual Subject

Possible reasons for discontinuing a subject from receiving study drug include:

1. Excessive toxicity as delineated by AE algorithms.

2. Any clinical adverse event, laboratory abnormality, intercurrent illness, other medical condition or situation that, in the opinion of the Sponsor's Medical Monitor or clinical site Investigator, continued participation in the study would not be in the best interest of the subject.

3. Study closure due to a decision by the regulatory authorities or Sponsor.

Subjects who discontinue study drug because of adverse events should be encouraged to complete visits through Day 98 and to complete the 6-week post-drug surveillance phase of the study.

9.2.2 Rules for Suspension of the Entire Study

Interim rules to halt enrollment until an ad hoc safety review is convened are based on simple proportionality, and are therefore:

Hematologic SAEs: Grade 3: >2 in 20 enrolled subjects,

Grade 3: >3 in 30 enrolled subjects,
Grade 4: Any.

Based on the known toxicity profile of the study drug, non-hematologic SAEs related to study drug are not likely to occur. Halting-rules for non-hematologic SAEs related to study drug are therefore not specified in this protocol. Instead, non-hematologic SAEs related to study drug will be reported to the Medical Monitor. The Medical Monitor will assess whether to convene an ad hoc review. The following are provided to the Medical Monitor as guideline thresholds to convene an ad hoc review, but they are not to be binding:

Non-Hematologic SAEs related to study drug:	Grade 3: >1 in 30 enrolled subjects, Grade 4: Any.

The objective of an ad hoc review would be to render a decision as to whether the study should continue per protocol, proceed with caution, be further investigated, be discontinued, or the trial be modified and then proceed. Suspension of enrollment for the entire study is a potential outcome of a safety review.

The review of serious, unexpected and related adverse events by the Medical Monitor, IRB, the Sponsor, and regulatory authorities may also result in suspension of further study drug administration. The regulatory authorities and the study sponsor retain the authority to suspend additional enrollment and study drug administration for the entire study as applicable.

10 STATISTICAL CONSIDERATIONS

This study is a 14 week double-blind, placebo-controlled, study to establish the efficacy of once weekly oral LD-AMT in the treatment of moderate-to-severe psoriasis. The co-primary endpoints are 1) the PASI 75, a composite measure; and 2) the Static Physician Global Assessment (sPGA) dichotomized to success or failure. The efficacy of LD-AMT will be established by comparing: 1) the proportion of subjects attaining a PASI 75 in the placebo arm and active LD-AMT arm; and 2) the proportion of subjects attaining a sPGA success (a score of 0 or 1) in the placebo arm and active LD-AMT arm. These comparisons will be made using the Fisher's exact test. The null hypothesis is no treatment effect or equality of proportions, and the alternative hypothesis is that 3 mg LD-AMT/week is effective at providing a greater proportion of PASI 75 than placebo, or that 3 mg LD-AMT/week is effective at providing a greater proportion of sPGA success than placebo.

All descriptive and inferential statistical analyses will be performed using SAS® version 9.3, R version 3.01, or Strata version 13 or higher. Descriptive statistics for continuous variables will consist of the mean, median, geometric mean (where appropriate), standard deviation, minimum, and maximum values. For categorical variables, the number and percentage of each category will be displayed for each treatment group. For the analysis of safety and immunogenicity endpoints, a two-sided alpha level of 5% will be used. All statistical tests will be two-tailed unless otherwise stated.

Demographics will be compared among treatment groups using Fisher's exact test for categorical variables and either a two-sided t-test or the Wilcoxon sum-rank test for continuous variables depending on the distribution of the underlying data. Calculations and statistical analyses will be described in further detail as part of a statistical analysis plan.

10.1 Determination of Sample Size

For the purpose of determining the sample size for this study, the sPGA results indicating the success and failure endpoint for placebo and antifolate treatment of psoriasis was not available. In contrast, PASI 75 endpoint results were available. Based on these results the proportion of PASI 75 achieved in subjects treated with placebo is assumed to be 15%, the proportion of PASI 75 achieved in subjects treated with 3.0 mg/week LD-AMT dose is assumed to be 60%, and using a significance level (2-sided alpha) of 0.05, giving a final sample size of 46 subjects. This sample size provides approximately 85% power to detect a statistically significant efficacy-response. The sample size was calculated assuming that a two-sided Fisher's exact test will be used to analyze the primary endpoint. Moderate loss to follow-up will still result in adequate power – the power would be approximately 80% assuming 10% loss to follow-up.

Sensitivity Analysis. ICH E9, "It is important to investigate the sensitivity of the sample size estimate to a variety of deviations from these assumptions and this may be facilitated by providing a range of sample sizes appropriate for a reasonable range of deviations from assumptions." The table below shows the sample size sensitivity analysis for a range of deviations in sample size, power and treatment effect size assuming a 2-sided alpha of 0.05 and a placebo PASI75 of 15% (power computed using http://hedwig.mgh.harvard.edu/sample_size/fisher/js/fisher.html).

			N		
PASI75	46	50	54	58	62
60%	0.85	0.89	0.91	0.93	0.95
55%	0.76	0.80	0.84	0.86	0.89
50%	0.64	0.68	0.73	0.76	0.80

Considering a power of 0.80 a minimum, the above sensitivity analysis supports a sample size expansion of up to 16 subjects based on a reasonable range of deviations in treatment PASI75 from assumptions.

10.2 Plan for Statistical Summaries and Analyses

10.2.1 General Considerations

Statistical summaries and analyses of baseline and safety data will be provided for the ITT and safety population, defined as all subjects who receive at least one dose of study drug. Statistical summaries and analyses of folate metabolism data will be provided for the ITT and per-protocol population, defined as subjects who meet the inclusion/exclusion criteria, receive all 14 study drug doses, and complete the Day 98 visit.

Comparisons will be made using a two sided 0.05 level of significance ($\alpha = 0.05$). The null hypothesis for the comparison is that there is no difference between the treatment groups. Pairwise comparison of 3.0 mg LD-AMT and placebo will be analyzed by Fisher's exact test for discrete binary comparisons. The primary efficacy analyses for the co-primary endpoints will be analyzed utilizing a step-down procedure, which determines statistical significance for the co-primary endpoints, while protecting the rate of type I error. The order of sPGA and PASI75 analysis in the

step-down procedure will be determined in the final statistical analysis plan prepared prior to unblinding. Continuous and categorical data will be analyzed according to t-test and Wilcoxon rank sum, respectively.

All individual subject data listings for safety endpoints and the primary metabolism endpoint will be provided in separate appendices to the clinical study report. Separate listings will be provided for each of the treatment groups. All statistical analyses will be performed using SAS® version 9.3, R version 3.01, or Stata version 131 or higher.

10.2.2 Disposition of Subjects

The following information will be summarized for each treatment group:

- Number of subjects randomized
- Number (%) of subjects receiving all 14 study drug doses
- Number (%) of subjects who discontinued the study and reasons for discontinuation
- Number (%) of subjects in the per-protocol population and reasons for those excluded
- Number (%) of subjects with at least one protocol deviation

Protocol deviations will be identified by the Syntrix Medical Monitor (or designee) for the trial.

10.2.3 Demographic Characteristics

The summaries and statistical analyses of demographic characteristics will be provided for the safety population.

10.2.4 Safety Endpoints

The summaries and statistical analyses of the safety endpoints will be completed for the safety population. Safety endpoints include AEs, any occurrence of dose-limiting toxicity, and changes in laboratory values. All AEs will be recorded by the Investigator in the AE CRF, and all AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

10.2.4.1 Adverse Events

All AE terms will be coded using MedDRA version 15 or higher. Summaries of the number (%) of subjects in each treatment group with at least one AE, classified according to MedDRA preferred term and system organ class, will be provided for:

- All AEs
- Related AEs
- SAEs

Related AEs are defined as AEs that are possibly, probably, or definitely related to study drug, as assessed by the study Investigator. The treatment groups will be compared with respect to the percentage of subjects with at least one AE using Fisher's exact test.

Comparisons of the treatment groups with respect to the incidence of AEs, classified according to preferred term and system organ class, will also be performed for all events reported by at least 5 subjects overall.

The following additional summaries of AEs will also be provided:

- Incidence of AEs by severity of event (mild, moderate, severe, potentially life-threatening)
- Incidence of AEs by relationship to study drug (unrelated, related)

10.2.4.2 Incidence of Dose-limiting Toxicity

The number (%) of subjects with at least one event of dose-limiting toxicity will be summarized for each treatment group.

10.2.4.3 Laboratory Data

Summaries of the actual value and change from baseline for all laboratory tests will be provided for each study visit. A tabulated summary of laboratory abnormalities by toxicity grade will also be provided.

10.2.4.4 Interim Safety Analyses

Interim safety reports will be produced during the study.

10.2.4.5 Missing Data

Missing efficacy data, safety data, and folate metabolism data will be recorded as they are without imputation of missing values.

10.3 Procedure for Deviations from Planned Statistical Analyses

The planned statistical analyses for this study will be described in detail in a statistical analysis plan. Modifications or additions to the analyses of study data will be described in the statistical analysis plan. Any decisions to deviate from the planned analyses described in the protocol will be documented in the clinical study report. The clinical study report will also provide a detailed explanation for any deviations from the planned analyses. The final statistical analysis plan prepared prior to unblinding is controlling in all respects, including for any differences between the final statistical analysis plan and any plan in any protocol.

11 ADMINISTRATIVE PROCEDURES

11.1 Institutional Review Board Approval

The experimental protocol for this study has been designed in accordance with principles of GCP and ICH E6. The review of this protocol by the IRB and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles codified in Title 21 CFR Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

11.2 Informed Consent

An IRB-approved study informed consent will be obtained from each subject that includes a description of: the investigational plan, including study procedures that include analysis of gene expression levels; specimen storage; risks and benefits; any study-related costs; and available alternative treatment options. The Investigator or his/her staff will explain the nature of the investigation and the risks involved to each subject prior to enrollment and will obtain written informed consent. The subject will also be informed that he/she is free to voluntarily withdraw from the study at any time.

11.3 Direct Access to Source Data/Documents, Study Monitoring, Data Collection

The Investigator will allow representatives of Syntrix (or their designee) to periodically monitor, at mutually convenient times during and after the study, all CRFs and corresponding source documents for each subject. The Principal Investigator is required to ensure that all CRFs are completed for every participant entered in the trial. It is important that the Investigator or staff is available at these visits. The monitoring visits provide Syntrix with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of CRFs, to resolve any inconsistencies in the study records, as well as assuring that all protocol requirements, applicable regulations, and Investigator's obligations are being fulfilled. The Investigator must maintain all source documents (i.e., all information, original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to clinical charts, laboratory notes, pharmacy dispensing records, and subject files and records kept at the pharmacy, at the laboratories, and other medico-technical departments involved in the clinical trial), for possible review. The investigational site will provide direct access to all trial-related source documents, other documents, and reports for the purpose of monitoring and auditing by Syntrix, NIH, and regulatory authorities.

The Syntrix representative will record the date of each monitoring visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the Investigator in writing. Telephone contact will be made as necessary during the data collection period and during the data and report writing periods.

Syntrix and representatives will develop study CRFs to ensure that: (1) all information needed for the primary and secondary analyses are being collected in a way that will allow accurate and complete analysis; (2) minimal extraneous information is being collected; and (3) the format is efficient for recording, entering and analyzing the data.

Syntrix or representatives will log and track CRFs to make sure that each CRF page received is processed in a timely manner. Each table in the database will be carefully checked to make sure that all the variables specified on the CRF have been appropriately entered into the database. Data will be cleaned using manual and automated data checks. Data cleaning queries will be sent to investigators, appropriate ancillary staff, and clinical research monitors. The status of data queries will be monitored. Syntrix or representatives will ensure that queries are promptly addressed. Syntrix or representatives will work collaboratively with clinical monitors to follow-up on data clarification, initiating communication with the clinical site when necessary to make sure that data problems are promptly addressed. This process will be used to generate clean data.

If CRF entries are modified the clinical site staff will annotate the working copy of the CRF with who made the change and the date the change was made. The clinical monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol and the applicable regulatory requirements.

Syntrix is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

11.4 Modification of the Protocol

No deviations from the protocol are permitted except in the event to avoid an immediate hazard to a study subject. Syntrix may approve minor exceptions on a case-by-case basis. If modification of the protocol is necessary, the modification must be initiated and confirmed in writing by Syntrix, and Syntrix will inform the IRB and the modification will not be implemented until approved by the IRB.

11.5 Protocol Deviation(s)

A protocol deviation is any noncompliance with the clinical trial protocol. Syntrix's Medical Director should be consulted if there is uncertainty as to whether a protocol deviation has occurred. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Protocol deviations will be recorded by the site on CRFs and included in the study database and final study report. It is the responsibility of the site to use continuous vigilance to identify and report deviations. Protocol deviations must be sent to the IRB per their guidelines.

11.6 Departure from the Protocol

A departure the protocol may be required if an emergency involving a subject occurs as permitted by ICH/GCP Guidelines 4.5.2, 4.5.4. The Investigator, or other physicians in attendance,

in such an emergency will, if circumstances and time permit, contact Syntrix immediately by telephone. The CRFs will completely describe the departure from the protocol and state the reasons for such departure. The IRB must be notified immediately if the departure from the protocol affects the safety or rights of the subject.

11.7 Suspension of the Study

If safety concerns arise during the study, the Sponsor may suspend, amend or terminate the study. Furthermore, if the study is suspended, the Sponsor may resume the study once the safety concern is resolved.

11.8 Study Termination by the Sponsor

Syntrix retains the right to terminate the study for any cause, suspending subject enrollment and removing all investigational products and related study materials from the study site at any time. Specific instances, which may precipitate such termination at a site, are as follows:

- Deviation from protocol requirements.
- Inaccurate or incomplete data recording on a recurrent basis.
- Unauthorized use of investigational products.
- Delinquent fulfillment of obligation on the part of the Investigator with regard to adverse reaction reporting, unacceptable subject enrollment, or other responsibilities as outlined in this protocol.

11.9 Use of Information and Publications

Publication of the results of this study is encouraged subsequent to full data analysis. No part of the results of the study, or any of the information provided by the Sponsor to the Investigator for the purposes of performing the study, will be published, or passed on to a third party, without prior review by the Sponsor. The Investigator, or anyone else working on the study, will submit all proposed publications, papers, abstracts or other written materials related to the Study, or an outline of any proposed oral presentation with respect thereto, to the Sponsor at least one month prior to (i) submission of such written materials for publication, or (ii) any proposed oral disclosure to a third party.

The Sponsor shall have the right to comment on such written material or outline; such comments shall be considered in good faith by the Investigator in determining the final form of disclosure. In the event patentable material is identified in the data, the Sponsor may delay publication for up to six months to submit the appropriate patent applications. Notwithstanding any of the above, the Investigator or anyone else working on the Study may not include any confidential information in any such publication or disclosure.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., Phase 1 trials), would be exempt from this policy. Syntrix will register this trial in a public trials registry.

The Investigator is obliged to provide the Sponsor with complete test results and all data derived from the study. Only the Sponsor may make information obtained during and from the study available to regulatory agencies, except as required by regulation.

11.10 Record Retention

The Investigator or Investigative site must retain the clinical study until a minimum of two years following the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the study agent. Syntrix Biosystems will notify sites when records can be destroyed. In the event this information is not communicated to the sites, permission must be obtained from Syntrix Biosystems before records can be destroyed.

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

Women comprise roughly half of all subjects with moderate-to-severe psoriasis although there tends to be a slightly greater female prevalence in the third decade of life. This is reflected in the subject population at this study's clinical sites. Thus, women are expected to make up roughly half of the study population.

Children and subjects less than 18 years of age are excluded from this phase 2 study. Thus, the study will not enroll children, pregnant women, prisoners, or other vulnerable populations. The study is therefore exempt from 45 CFR 46 Subparts B, C and D.

11.12 Subject Confidentiality

Subject confidentiality will be maintained, and neither full names nor social security numbers will be entered into the database. Subject confidentiality will be strictly held in trust by the participating Investigators and their staff, and the Sponsor and their representatives.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the Sponsor.

Appendix A: Schedule of Study Visits and Procedures

[1] At each visit study drug is counted and a single dose can be taken if it maintains the exact weekly administration cycle

Procedure	Screen	Treatment Phase					Post-Treatment Phase	
	Days -30 to 0	Day 0	Day 14(±2)	Day 42(±3)	Day 70(±3)	Day 98(±3)	Day 119(±4)	Day 140(±4)
		Week 0	Week 2	Week 6	Week 10	Week 14	Week 17	Week 20
Randomization		X						
Study Drug Dispensed		X						
Study Drug Administer[1]		X	X	X	X			
Clinical								
Informed Consent	X							
Contraception Requirements[2]	X	X	X	X	X	X	X	X
Medical History & Physical Exam	X	X[3]		X[3]	X[3]	X[3]		
Chest X-ray	X							
Vital Signs	X	X				X		
Assess Psoriasis BSA involvement	X							
PASI	X	X				X		
sPGA		X				X		
Dermatology Life Quality Index		X				X		
Review Patient Diary			X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Safety Lab Tests								
CBC with Differential	X		X	X	X	X		
Chemistries[4]	X		X	X	X	X		
HIV1/2, Hepatitis B & C Serology	X							
UA	X					X		
Pregnancy Test[5]	X	X	X	X	X	X		X
Folate Metabolism Studies								
Collect Blood[6]		X						

of study drug.

[2] Contraception is to be used while on study and for 90 days after the last study drug dose.

[3] Physical exam performed as directed and required by interim history.

[4] Chemistries include BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, albumin and total protein.

[5] Urine pregnancy tests for women of child-bearing potential only. Tests will be performed during subject's visit, prior to dosing.

[6] The specific amount of blood will be indicated and processed as described in study specific procedures.

Appendix B. Calculation of Selected Inclusion and Exclusion Criteria

1. Inclusion Criteria: Creatinine Clearance Estimate by Cockcroft-Gault Formula

$$\text{creatinine clearance} = \frac{[(140 - \text{age}) \times \text{weight}]}{72 \times \text{SCR}}$$

where, age is in years
weight is in kg
serum creatinine (S_{CR}) is in mg/dL.
creatinine clearance is ml/min

in females, the result is multiplied by 0.85 (Cockcroft '76). The Cockcroft-Gault value is not adjusted for body surface area (BSA), and in this protocol must be equal to or greater than 60 ml/min. An online Cockcroft-Gault calculator is available at: http://nephron.com/cgi-bin/CGSI.cgi .

Appendix C. Toxicity Grading Scale for Clinical Laboratory Value [1]

	Grade			
Adverse Event	**1**	**2**	**3**	**4**
WBC decreased	< LLN – 3,000/mm3	<3,000 – 2,000/mm3	<2,000 – 1,000/mm3	<1,000/mm3
Anemia	Hemoglobin (Hgb) <LLN – 10.0 g/dL	Hgb <10.0 – 8.0 g/dL	Hgb <8.0 g/dL	Life-threatening consequences; urgent intervention indicated
Platelet count decreased	< LLN – 75,000/mm3	<75,000 – 50,000/mm3	<50,000 – 25,000/mm3	< 25,000/mm3
AST (SGOT) increased	> ULN – 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20 x ULN	> 20 x ULN
ALT (SGPT) increased	> ULN – 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20 x ULN	> 20 x ULN
Alkaline phosphatase increased	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	>5.0 - 20 x ULN	> 20 x ULN
Total bilirubin increased	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	>3.0 - 10 x ULN	> 10 x ULN
Hypoalbuminemia	<LLN – 3 g/dL	<3 – 2 g/dL	<2 g/dL	Life-threatening consequences; urgent intervention indicated

[1] US Dept. of Health and Human Services, NIH, NCI, Common Terminology Criteria for Adverse Events, Version 4.0 28 May 2009 (v4.03, 14 June 2010). ULN=upper limit of normal; LLN=lower limit of normal; Hgb=hemoglobin;

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