## 1.0 PROTOCOL

Study Title: An Investigator-Initiated, Assessor Blinded, Randomized Study Comparing the Mechanism of Action of Adalimumab to Methotrexate in Subjects with Moderate to Severe Chronic Plaque Psoriasis.

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## 1.1 PROTOCOL SYNOPSIS

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| Trial design | Assessor Blinded, Randomized |
| Rationale | Both methotrexate and adalimumab are FDA-approved drugs for the treatment of moderate to severe psoriasis. In the CHAMPION Study, more adalimumab-treated, moderate to severe psoriasis patients achieved a PASI 75 after 16 weeks compared to those treated with methotrexate. The reason for this difference is poorly understood. There are no direct comparative mechanism of action studies in psoriasis patients comparing adalimumab with methotrexate. |
| Hypotheses | In plaques from psoriasis patients treated with adalimumab compared with methotrexate:<br><br>1. Adalimumab suppresses IFN-γ gene expression in plaques in a higher proportion of patients than does methotrexate.<br>2. Adalimumab suppresses TIP-dendritic cell and Th17-associated genes, e.g. IL-23, IL-22, IL-17 gene expression, in plaques in a higher proportion of patients than does methotrexate.<br>3. Adalimumab suppresses epidermal hyperplasia-associated genes, e.g. IL-22, K-16 keratin in a higher proportion of patients than does methotrexate.<br>4. Adalimumab suppresses inducible nitric oxide synthase (iNOS) in plaques in a higher proportion of patients than does methotrexate. |
| Inclusion Criteria | 1. Adults 18 to 85 years of age with moderate to severe psoriasis, in general good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, and physical examination, and who are candidates for systemic or photo therapy.<br>2. Presence of a psoriatic plaque of 2 cm or greater in an area which can be biopsied repeatedly.<br>3. Because patients may receive methotrexate, women are eligible to participate in the study if they meet one of the following criteria:<br>A. Women of childbearing potential must undergo monthly pregnancy testing while on methotrexate and at the beginning and end of the study, and agree to use two of the following methods of contraception throughout the study and for 90 days after the last dose of methotrexate:<br>○ Oral contraceptives; |

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| | ○ Transdermal contraceptives;<br>○ Injectable or implantable methods;<br>○ Intrauterine devices; and<br>○ Barrier methods (diaphragm with spermicide, condom with spermicide).<br><br>Abstinence and Tubal Ligation are also considered a form of Birth control.<br><br>B. Women who are postmenopausal (for at least one year), sterile, or hysterectomized.<br>4. Because patients may receive methotrexate, men must agree to avoid impregnating a woman while on this study and for 90 days after the last methotrexate dose. |
| Exclusion Criteria | 1. Patients <18 years old or >85 years old<br>2. Absence of a psoriatic plaque at least 2 cm in diameter<br>3. Active guttate, erythrodermic, or pustular psoriasis at the time of the screening visit<br>4. Evidence of skin conditions at the time of the screening visit (e.g. eczema) other than psoriasis that would interfere with evaluations of the effect of study medication on psoriasis<br>5. Inability to understand the consent process<br>6. Receipt of any investigational drugs or biologics within 4 weeks of study drug initiation<br>7. PUVA or oral systemic treatments within 4 weeks of study drug initiation.<br>8. Biologics within 3 months of study initiation<br>9. UVB therapy within 2 weeks of study drug initiation<br>10. Topical steroids, topical vitamin A or D analog preparations or anthralin within 2 weeks of study drug initiation. (Exception - topical steroids at no higher than moderate strength, are permitted on scalp, axillae, and groin but dose and formulation must be kept stable throughout trial.)<br>11. Methotrexate within 6 weeks of study initiation<br>12. History of prior treatment with adalimumab<br>13. History of primary non-response to methotrexate, infliximab or etanerecpt<br>14. History of prior discontinuation of methotrexate or a TNF antagonist for a safety-related reason that makes it unwise to restart either type of drug<br>15. Any internal malignancy within 5 years (fully excised cutaneous, basal cell carcinoma or squamous cell carcinoma are exceptions)<br>16. Pregnancy, not practicing effective birth control, or inability to practice safe sex during the length of the study<br>17. Lactation |

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| | 18. Subjects who have known hypersensitivity to adalimumab or methotrexate or any of their components<br>19. History of alcohol or drug abuse one year before and during the study.<br>20. Known HIV-positive status or any other immune-suppressing disease.<br>21. Presence of a grade 3 or 4 infection <30 days prior to the screening visit, between the screening visit and the first day of treatment on study, or any time during the study that in the opinion of the Investigator would preclude participation in the study.<br>22. Any grade 3 or 4 adverse event, or laboratory toxicity, at the time of the screening visit or at any time during the study, which in the opinion of the Investigator, would preclude participation in the study.<br>• Serum creatinine $\geq$ 3.0 mg/dL (265 micromoles/L)<br>• Serum potassium < 3.5 mmol/L or $\geq$ 5.5 mmol/L<br>• Serum ALT or AST $\geq$ 3 times the upper limit of normal for the Lab<br>• Platelet count < 100,000/$mm^3$<br>• WBC count < 3,000 cells/$mm^3$<br>• Hemoglobin, hematocrit, or red blood cell count outside 30% of the upper or lower limits of normal for the Lab<br>23. Receipt of live vaccines 1month prior to or while on study<br>24. A prior history of tuberculosis, and/or a positive PPD skin test/CXR at screening without appropriate treatment.<br>Treatment of latent TB infections (for those with positive PPD tests) must be initiated prior to therapy with adalimumab or methotrexate.<br>25. Chronic hepatitis B or hepatitis C infection, history of multiple sclerosis, transverse myelitis, optic neuritis or epilepsy. |
| Subject Cohorts | 2 cohorts (Randomized 1:1 adalimumab:methotrexate) (patients who are naive to both methotrexate and anti-TNF therapy will be equally distributed between methotrexate and adalimumab arms):<br>15 adalimumab-treated patients<br>15 methotrexate-treated patients who will then receive 16 weeks of adalimumab at the end of study. |
| Number of Subjects | 30 |
| Histologic Endpoints | Immunohistochemistry: Histological markers will be studied, including K16, CD3, CD11c, DC-LAMP, CD163, CD161, BDCA-1, TRAIL, and epidermal thickness. Other possible markers, to be decided, include Langerin, CD4, CD8, FOXP3, elastase, and BDCA-2. At baseline (lesional and uninvolved skin), weeks 1, 2, 4, and 16 (lesional only) |

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| | mRNA gene expression: by RT-PCR (normalized to HARP) of IL-1, IL-6, IL-8. iNOS, p19 and p40 subunits of IL-23, IL-20, IFN-γ, IL-17A, IL-22, defensin-beta2, CCL-20, and MX-1 at baseline (lesional and uninvolved skin), weeks 1, 2, 4, and 16 (lesional only). Gene arrays will be performed on a small subset of patients depending on responses seen for (above) RNA expression. |
| Clinical Endpoints | Clinical Endpoints (screen, baseline, week 1, week 2, monthly):<br>PASI<br>PGA<br>BSA<br>Target lesion scoring and photography of lesional biopsy site |
| Duration of Trial | 16 weeks for study followed by 16 weeks of adalimumab for only the previous methotrexate-treated patients |
| Adverse Event Monitoring | Refer to schedule of assessments |
| Laboratory Tests | 1. PPD (and CXR if indicated), Hepatitis B and C at screening<br>2. Urine Pregnancy Test at Screening, Baseline, monthly for methotrexate treated patients through week 16, and at Screening, Baseline and at week 16 for adalimumab treated patients<br>3. For adalimumab cohort: CBC, complete metabolic profile, CRP, ANA at Screening and 16 weeks after initiation of adalimumab<br>4. For methotrexate cohort: CBC, complete metabolic profile, CRP at Screening and at week 16, 32; ANA at Screening and week 16.<br>5. For methotrexate cohort: CBC, LFT, lytes, BUN, Cr after screening, weekly until stable dose is reached, then monthly until week 16<br>6. Vital signs and physical examination at Screening, Baseline and monthly.<br>7. Adverse events assessment at Screening, Baseline and monthly. |
| Biopsy of lesions | At baseline (lesional and non-lesional), weeks 1, 2, 4, and 16 (lesional only) |
| Statistical Considerations | Descriptive study |

## 1.2 BACKGROUND INFORMATION:

### 1.2.1 Proposed Indication and Study Rationale

Psoriasis is a hyperproliferative, inflammatory, immune-mediated skin disease that affects approximately 2% of the United States and European populations (Tutrone 2001, Kipnis 2005). This disease manifests as red, scaly plaques that are itchy and/or painful. Patients with psoriasis may be socially stigmatized because of their appearance. Currently, there is no cure for this

condition. Often, repeated medical treatments are necessary and can become expensive. Treatment with topical corticosteroids is the mainstay therapy for mild to moderate psoriasis. In more severe cases, systemic therapies (e.g., cyclosporine, methotrexate, acitretin, TNF blockers (adalimumab, infliximab, etanercept) and phototherapy (e.g., UVB irradiation)) are used.

Both methotrexate and adalimumab are FDA-approved drugs for the treatment of moderate to severe psoriasis. The two treatments, methotrexate and adalimumab, both show efficacy for psoriasis, however their profiles differ. In the CHAMPION Study, more adalimumab-treated, moderate to severe psoriasis patients achieved a PASI 75 after 16 weeks compared to those treated with methotrexate (80% vs. 36%)(Saurat 2007). The reason for this difference is poorly understood. No direct comparative mechanism of action studies in psoriasis patients between methotrexate and adalimumab (or any TNF blocker) has been reported.

With etanercept, another TNF blocker, the in vivo mechanism has been studied with some scientific rigor. These studies demonstrate that etanerecpt down regulates multiple pro-inflammatory pathways (Table 1) resulting in:

1. Decreased myeloid dendritic cell activation and maturation;
2. Decreased T cell (Th1 and Th17) activation;
3. Decreased NFκB activation;
4. Decreased cytokine (e.g. IFN γ, IL-23, IL-22, IL-17), growth factor and chemokine production by multiple cell types;
5. Introduction of apoptosis in dermal myeloid dendritic cells in only responding patients.

To date, there are no similar studies with adalimumab or methotrexate.

In order to understand the molecular and cellular basis for the differential clinical efficacy of adalimumab and methotrexate, it is essential to compare their mechanisms of action in psoriatic plaques.

### 1.2.2 Biomarkers in Psoriatic Plaques

Studies of the pathogenesis and treatment of psoriasis have greatly benefited from the fact that both psoriatic plaques and uninvolved skin are accessible to repeated biopsy. These studies demonstrated important pathogenic roles of Th17 and Th1 cells, plasmacytoid and myeloid dendritic cells, activated endothelial cells, and keratinocytes bearing the regenerative maturation phenotype.[1-12] Immunocytochemistry, flow cytometry, RT-PCR, and DNA array analyses have generated large lists of biomarkers, some of which have been validated in clinical trials with cyclosporine, phototherapy, calcipotriol, corticosteroids, retinoids, 6-thioguanine, alefacept, efalizumab, etanerecpt, and infliximab (Table 1).[4,5,7,13-26, 34-35] Biomarkers have been used as surrogate treatment endpoints in early, short term, proof-of-concept studies.[19,27,28]

Immunocytochemical biomarkers include those identifying members of the inflammatory infiltrate (e.g. T cells, dendritic cells, neutrophils, macrophages), transcription factors (e.g. activated NFκB), markers of keratinocyte activation or regenerative maturation (Keratin K-16, Ki-67, filaggrin, involucrin, epidermal thickness, I-CAM-1, and HLA-DR expression). RT-PCR demonstrated increased mRNA expression of multiple chemokines (e.g. IL-8, MIG, IP-10, and

MIP3α), cytokines (e.g. IL-12, IL-23, IFN γ, IL-6, IL-1β, IL-8, IL-22, and IL-20) nuclear transcription factors (NFκB, STAT-1), metalloproteinases (MMP-12), antimicrobial peptides, and keratin K-16 in psoriasis. DNA array identified over 1300 genes differentially expressed in psoriatic plaques vs. non-lesional skin.[29]

Table 1: Change of Expression of Selected Biomarkers in Clinical Trials of Biologics in Psoriasis Vulgaris

| Biomarker | Etanercept[1,30-32,34-35] | Infliximab[25,33] | Alefacept[25,33] | Efalizumab[25,33] |
|---|---|---|---|---|
| | | | | |
| CD3 | Decreased | Decreased | Decreased | Decreased |
| CD4 | Decreased | Decreased | Decreased | Decreased |
| CD8 | Decreased | Decreased | Decreased | Decreased |
| CD11c (myeloid DCs) | Decreased | Decreased | Decreased | Decreased |
| CD83 | Decreased | ND | Decreased | Decreased |
| Elastaste (Neutrophils) | Decreased | ND | ND | ND |
| iNOS | Decreased | ND | Decreased | Decreased |
| IL-12/23p40 | Decreased | ND | Decreased | ND |
| IL-23 p19 | Decreased | ND | Decreased | ND |
| IL-22 | Decreased | ND | ND | ND |
| IL-17 | Decreased | ND | ND | ND |
| IFNγ | Decreased | ND | Decreased | ND |
| STAT-1 | Decreased | ND | Decreased | ND |
| IP-10 | Decreased | ND | ND | ND |
| MIG | Decreased | ND | Decreased | ND |
| Granzyme B | Decreased | ND | ND | ND |
| Keratinocyte ICAM-1 and/or HLA-DR* | Decreased | Decreased | Decreased | Decreased |
| IL-6 | Decreased | ND | ND | ND |
| IL-1β | Decreased | ND | ND | ND |
| IL-8 | Decreased | ND | Decreased | ND |
| MIP-3α | Decreased | ND | ND | ND |
| Activated NFκB | Decreased | ND | ND | ND |
| IL-20 | Decreased | ND | ND | ND |
| MMP-12 | Decreased | ND | ND | ND |
| Keratin K-16 | Decreased | Decreased | Decreased | Decreased |
| Epidermal Thickness | Decreased | Decreased | Decreased | Decreased |
| Cleaved Caspase-3 | Increased | Increased | Increased | ND |

ND = Not Done

*Decreased = decreased or absent

We will study the following biomarkers in this proposal with immunohistochemistry: K16 (and epidermal thickness), CD3, CD11c, and DC-LAMP (all markers that change significantly with etanercept). Measures are for regenerative epidermal maturation, T-cells, myeloid dendritic cells, and mature dendritic cells (DCs), respectively. Other markers include CD163 (for macrophages), CD161 (for NK or NK-like T-cells), BDCA-1 (for the skin-resident population of myeloid DCs), and TRAIL (which marks the inflammatory population of myeloid DCs). The number of macrophages (CD163) is slightly elevated in psoriasis lesions and might decrease with treatment; TRAIL is a more consistent IHC marker than iNOS or TNF. Other possible markers, to be decided, include Langerin (for Lanherhans cells), CD4, CD8, FOXP3, elastase, and BDCA-2.

At least 3 inflammatory "elements" are regulated by TNF and appear in the set of gene changes induced by etanercept. These are 1) the classical "sepsis" cytokines regulated by TNF through NFkB-- IL-1, IL-6 and IL-8; 2) products of inflammatory DCs or TIP-DCs, which include iNOS, p19 and p40 subunits of IL-23, IL-20; and 3) Th1 and Th17 T-cell subsets, for which relevant genes include interferon-gamma, IL-17A and IL-22. We will also measure defensin-beta2 and CCL-20 (as downstream genes of IL-17 activation) and MX-1 (as a downstream gene of interferon (STAT1) activation). We will use HARP mRNA as a housekeeping gene to normalize expression for each of the above genes.

The directed analysis for RNA expression (above) targets genes which are likely to be regulated by a TNF inhibitor (adalimumab). Methotrexate might have a very different set of genes regulated. As such, a broad analysis of gene expression via a gene array may be the most informative and complementary to gene measures by real-time PCR. A number of inflammatory genes are not well detected on arrays, due to sensitivity, so good measures of T-cell cytokines and IL-23 are best done via RT-PCR. However, gene arrays do provide the broad overview that may be critical in finding different mechanisms of action of methotrexate vs. TNF inhibition. Gene arrays will be performed a small subset of patients depending on responses seen for (above) RNA expression.

### 1.2.3 Adalimumab

Adalimumab is indicated and FDA approved for treatment of several autoimmune diseases, including moderate to severe psoriasis. Adalimumab is a fully human monoclonal antibody against tumor necrosis factor alpha (TNF-α). It is typically administered with subcutaneous injections in an outpatient setting with dosing intervals of 2 weeks.

Potential risks of therapy with adalimumab, or other TNF inhibitors, include serious infections (including TB, invasive fungal, and other opportunistic infections); hypersensitivity reactions; injection site reactions; immunogenicity; autoimmunity; demyelinating disease; and malignancy.

### 1.2.4 Methotrexate

Methotrexate is indicated and FDA approved as an anti-metabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis. It is typically administered as a tablet in an outpatient setting with an interval of 1 week.

Potential risks of therapy with methotrexate include serious infections (including TB, invasive fungal, and other opportunistic infections); bone marrow suppression; hepatotoxicity; gastrointestinal effects; hypersensitivity reactions; overdose; teratogenicity; immunogenicity; autoimmunity; and malignancy.

## 1.3 OBJECTIVES:

The objective of this study is to compare the mechanism of action between adalimumab and methotrexate in subjects with psoriasis.

### 1.3.1 Biologic Activity Endpoints

**1.3.1.1 Histologic endpoints**:
Immunohistochemistry: 10 histological markers will be studied, including K16, CD3, CD11c, DC-LAMP, CD163, CD161, BDCA-1, and TRAIL. Other possible markers, to be decided, include Langerin, CD4, CD8, FOXP3, elastase, and BDCA-2. At baseline (lesional and uninvolved skin), weeks 1, 2, 4, and 16.

Relative mRNA gene expression (normalized to HARP) of IL-1, IL-6, IL-8, iNOS, p19 and p40 subunits of IL-23, IL-20, IFN-γ, IL-17A, IL-22, defensin-beta2, CCL-20, and MX-1 at baseline (lesional and uninvolved skin), weeks 1, 2, 4, and 16. Gene arrays will be performed a small subset of patients depending on responses seen for (above) RNA expression.

**1.3.1.2 Clinical endpoints:**
Clinical Endpoints (screen, baseline, week 1, week 2, monthly):

- PASI
- PGA
- BSA
- Target lesion scoring and photography of lesional biopsy site

## 1.4 STUDY DESIGN:

### 1.4.1 Description of the Study

This is a Post-Marketing Observational Study (PMOS), investigator-initiated, lab assessor-blinded, study comparing the mechanism of action of adalimumab vs. methotrexate in the treatment of moderate to severe chronic plaque psoriasis in adults. It is designed to demonstrate measurable differences of biological markers in psoriatic plaques.

Adalimumab, marketed by Abbott Laboratories, (40mg per syringe; pre-filled syringes) will be used for injection. Methotrexate tablets 2.5 mg per capsule, will be used for oral dosing.

This will be an open label study using adalimumab and methotrexate. There will be two cohorts, and randomization will be 1:1 adalimumab:methotrexate. Patients who are naive to both methotrexate and anti-TNF therapy will be equally distributed between methotrexate and adalimumab arms. There will be 15 adalimumab-treated patients and 15 methotrexate-treated

patients who will then receive 16 weeks of adalimumab at the end of study. The study will last 16 weeks comparing adalimumab and methotrexate, followed by 16 weeks of adalimumab treatment for the previously methotrexate-treated patients. During methotrexate dosing folic acid (5 mg PO once per week) will be administered to the methotrexate-treated patients.

Laboratory assessors are blinded to treatment. The study pharmacist will randomize subjects after screening to either adalimumab or methotrexate.

Dosing will be on day 1 and then weekly. For the injections, dosing will occur according to product recommendations. Patients will receive 80mg adalimumab (2 pre-filled syringes, each with 40mg) on day 1, and then 40mg on week 1 and then every 2 weeks (from week 1 through week 15). For methotrexate dosing, patients will be dosed according to the CHAMPION study in single weekly doses of methotrexate: 7.5mg at week 0, increased to 10mg at week two, and increased to 15mg at week 4 for all patients. For oral dosing, if the PASI did not decrease by 50% at week 8, dosing will increase to 20mg per week; the dose will be maintained at 15mg per week if the PASI decreased by 50% or more at week 8. If the PASI did not decrease by at least 50% at week 12, oral dosing will increase to 25mg per week and will be maintained there. The methotrexate dose will be maintained at 20mg per week if the PASI decreased by 50% or more at week 12. All patients on methotrexate will also receive a dietary supplement of oral folate (5mg per week) beginning 48 hours after initiation of oral dosing and continued weekly thereafter on non-methotrexate dosing days.

After treatment on Day 1 the evaluation period will last 16 weeks. Subjects will have assessments at the screening visit, at the baseline visit, week 1, week 2, and then monthly visits. These assessments include VS, PE, PGA, PASI, BSA, Target Lesion Scoring (**Appendix B**), and photography of lesional biopsy site. If a subject meets eligibility criteria at screening and no wash-out period is necessary, baseline visits may occur as soon as the laboratory data are received.

PPD (and CXR if indicated), and Hepatitis B and C will be checked at screening. Urine Pregnancy Test will be checked at screening, baseline, and monthly for methotrexate treated patients through week 16, and at screening, baseline and at week 16 for adalimumab treated patients. For adalimumab cohort: CBC, complete metabolic profile, CRP, and ANA will be checked at screening and 16 weeks after initiation of adalimumab. For methotrexate cohort: CBC, LFT, complete metabolic profile, and CRP will be checked at screening and at weeks 16 and 32. For methotrexate cohort: CBC, LFTs, lytes, BUN, Cr will be checked after screening, then weekly until stable dose is reached, and then monthly until week 16. Vital signs and physical examination will be done at screening, baseline, and monthly. Adverse events assessment will be done at screening, baseline, and monthly. Skin biopsies will be done at baseline, week 1, week 2, week 4, and week 16. (**Appendix A**).

### 1.4.2 Rationale for the Study

Both methotrexate and adalimumab are FDA-approved drugs for the treatment of moderate to severe psoriasis The two treatments, methotrexate and adalimumab both show efficacy for psoriasis, however their profiles differ. In the CHAMPION Study, more adalimumab-treated, moderate to severe psoriasis patients achieved a PASI 75 after 16 weeks compared to those

treated with methotrexate (80% vs. 36% after 16 weeks) (Saurat 2007). The reason for this difference is poorly understood. No direct comparative mechanism of action studies in psoriasis patients between methotrexate and adalimumab (or any TNF blocker) has been reported.

### 1.4.3 Outcome Measures

#### 1.4.3.1 Histologic Outcome Measures

The following primary biologic activity outcome measure will be evaluated:

- Immunohistochemistry: Histological markers will be studied, including K16, CD3, CD11c, DC-LAMP, CD163, CD161, BDCA-1, TRAIL, and epidermal thickness. Other possible markers, to be decided, include Langerin, CD4, CD8, FOXP3, elastase, and BDCA-2. At baseline (lesional and uninvolved skin), weeks 1, 2, 4, and 16 (lesional only)
- Relative mRNA gene expression (normalized to HARP): of IL-1, IL-6, IL-8, iNOS, p19 and p40 subunits of IL-23, IL-20, IFN-γ, IL-17A, IL-22, defensin-beta2, CCL-20, and MX-1 at baseline (lesional and uninvolved skin), weeks 1, 2, 4 and 16 (lesional only). Gene arrays will be performed a small subset of patients depending on responses seen for (above) RNA expression.

#### 1.4.3.2 Clinical Outcome Measures

The following secondary clinical outcome measures will be evaluated at screen, baseline, week 1, week 2, and then monthly:

- PASI
- PGA
- BSA
- Target lesion scoring
- Photography of lesional biopsy site

#### 1.4.3.3 Safety Outcome Measures

All adverse events (AEs) will be recorded and monitored. At each of the study visits, patients will be questioned about the occurrence of new AEs since the last visit, or the outcome of any AEs that were reported at previous visits. Please refer to the FDA Package inserts that accompany this protocol for complete and updated safety information for both adalimumab and methotrexate. Please refer to Appendix A for complete schedule of study assessments.

### 1.4.4 Adverse Events & Safety Plan

#### 1.4.4.1 Injection Site Reactions

Injection of adalimumab may cause injection site pain, irritation bruising, swelling, and/or erythema. Some bleeding may occur. Subjects will be asked to rotate injection sites (between the abdomen and lateral thighs) to minimize these injection reactions.

#### 1.4.4.2 Infections

Patients will be screened for infections, including with a Complete Blood Count and screen tests for Hepatitis B and C, prior to enrolling in this study. Treatment with adalimumab or methotrexate should not be initiated in patients with active infections including chronic or localized infections. Investigators should exercise caution when considering the use of adalimumab or methotrexate in patients with a history of recurrent infections or underlying

conditions which may predispose them to infections, including those patients who have resided in regions where Tuberculosis and Histoplasmosis are endemic.

Patients who develop a new infection during treatment with adalimumab or methotrexate should be monitored closely until the infection resolves, and appropriate medical therapy should be initiated. Adalimumab injections should not be given to a patient with a clinically relevant, active infection. If a patient develops a serious infection (see section 1.6.1), discontinuation of adalimumab or methotrexate treatment must be considered.

#### 1.4.4.3 Screening for and Early Detection of Active Tuberculosis

Patients will be evaluated for latent tuberculosis (TB) infection with a tuberculin skin test (PPD), and all patients will have a chest x-ray (CXR) in screening. Treatment of latent TB infections (for those with positive PPD tests) should be initiated prior to therapy with adalimumab or methotrexate. This prophylaxis will be in accordance with the Centers for Disease Control current guidelines. Investigators should exercise caution with patients who have resided in regions where TB is endemic. Patients with an occupational or travel pattern that increases their likelihood of experiencing frequent contact with TB-positive individuals should not be enrolled in this study.

During the study, patients will be instructed to seek medical attention if signs or symptoms suggestive of a tuberculosis infection occur (e.g., persistent cough, wasting/weight loss, low grade fever). They will be also questioned with the following questions during the study:

- "Have you had a new cough of > 14 days' duration or a change in a chronic cough?"
- "Have you had any of the following symptoms:
  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?"
- "Have you had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If questioning during the study raises suspicion that a patient may have TB reactivation or a new TB infection, a prompt and complete investigation should be undertaken, including, when possible, consultation with a physician specializing in TB.

Assessors should be aware that TB reactivation may present as disseminated disease or with extra pulmonary features in an immunocompromised patient. Patients with evidence of active TB or newly diagnosed active or latent TB must immediately discontinue adalimumab or methotrexate and should be referred for appropriate treatment.

Patients who experience close contact with an individual with active TB during this study must have testing for latent TB that may include, but is not limited to the following: a chest radiograph, a repeat tuberculin skin test, and, if clinically appropriate, referral to a physician specializing in TB to determine the patient's risk of developing active TB and whether treatment for latent TB is warranted.

#### 1.4.4.4 Vaccinations

No data are available on the effects of vaccination in patients receiving adalimumab or methotrexate. However, live vaccines should not be given concurrently with adalimumab or methotrexate and patients will be advised against receiving a live vaccine during this study. They will also be screened for this and will not be allowed to participate if having received recent live vaccines.

#### 1.4.4.5 Methotrexate Organ System Toxicity

In general, the incidence and severity of acute side effects are related to dose and frequency of administration. The most serious reactions are discussed below under specific organ systems. That section, along with the FDA package insert, should also be consulted when looking for information about adverse reactions with methotrexate. Please see FDA package insert, included with protocol, for complete listing of organ system toxicities. Please also see the complete schedule of study assessments in Appendix A.

**Hematologic**: Unexpectedly severe (sometimes fatal) bone marrow suppression and aplastic anemia have been reported. This has also been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs (NSAIDs).

CBC will be checked after screening, then weekly until stable dose is reached, and then monthly until week 16. Methotrexate should be stopped immediately if there is a significant drop in blood counts. Patients will not be able to enroll or will be discontinued form the study with the following CBC parameters: Platelet count < 100,000/$mm^3$, WBC count < 3,000 cells/$mm^3$, or hemoglobin, hematocrit, or red blood cell count outside 30% of the upper or lower limits of normal for the Lab.

Patients will also be advised to avoid NSAIDs while on methotrexate.

**Hepatic**: Methotrexate has the potential for acute (elevated transaminases) and chronic (fibrosis and cirrhosis) hepatotoxicity. Chronic toxicity is potentially fatal; it generally has occurred after prolonged use (generally two years or more) and after a total dose of at least 1.5 grams. In studies in psoriatic patients, hepatotoxicity appeared to be a function of total cumulative dose and appeared to be enhanced by alcoholism, obesity, diabetes and advanced age. An accurate incidence rate has not been determined; the rate of progression and reversibility of lesions is not known.

LFTs will be checked after screening, then weekly until stable dose is reached, and then monthly until week 16. Patients will also be screened for Hepatitis B and C during screening, and will not be eligible to enroll if positive. Patients will not be able to enroll or will be discontinued form the study with the following LFT parameters: serum ALT or AST $\geq$ 3 times the upper limit of normal for the Lab.

**Gastrointestinal**: gastrointestinal toxicity has been reported with concomitant administration of methotrexate (usually in high dosage) along with some nonsteroidal anti-inflammatory drugs

(NSAIDs). Diarrhea and ulcerative stomatitis should require interruption of therapy; otherwise, hemorrhagic enteritis and death from intestinal perforation may occur.

Patients will also be advised to avoid NSAIDs while on methotrexate.

**Pulmonary**: Pulmonary symptoms (especially a dry nonproductive cough) or a nonspecific pneumonitis occurring during methotrexate therapy may be indicative of a potentially dangerous lesion and require interruption of treatment and careful investigation. Although clinically variable, the typical patient with methotrexate induced lung disease presents with fever, cough, dyspnea, hypoxemia, and an infiltrate on CXR.

Investigators should assess for possible pulmonary infection in those patients where suspicions are raised. This includes, but is not limited to, a CXR.

**Renal**: Methotrexate may cause renal damage that may lead to acute renal failure. Nephrotoxicity is due primarily to the precipitation of methotrexate and 7-hydroxyMethotrexate in the renal tubules.

Metabolic profile, lytes, BUN, and Cr will be checked after screening, then weekly until stable dose is reached, and then monthly until week 16. Patients will not be able to enroll or will be discontinued form the study with the following Renal parameters: serum creatinine $\geq$ 3.0 mg/dL (265 micromoles/L) or serum potassium < 3.5 mmol/L or $\geq$ 5.5 mmol/L.

**1.4.4.6 Overdose**

**Adalimumab Overdose:**

The maximum tolerated dose of adalimumab has not been established in humans. Multiple doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In cases of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

Patients will only be given enough adalimumab to use between study visits to prevent accidental overdose.

**Methotrexate Overdose**:

In post-marketing experience, overdose with methotrexate has generally occurred with oral administration.

Reports of oral overdose often indicate accidental daily administration instead of weekly (single or divided doses). Symptoms commonly reported following oral overdose include those symptoms and signs reported at pharmacologic doses, particularly hematological and gastrointestinal reactions. For example, leukopenia, thrombocytopenia, anemia, pancytopenia, bone marrow suppression, mucositis, stomatitis, oral ulceration, nausea, vomiting, gastrointestinal ulceration, gastrointestinal bleeding. In some cases, no symptoms were reported. There have been reports of death following overdose. In these cases, events such as sepsis or septic shock, renal failure, and aplastic anemia were also reported.

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered over dosages of methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

To help prevent accidental overdose, patients will only be given enough methotrexate to last until the next study visit.

In those patients suspected of having an overdose, immediate medical attention is required. Patients will be assessed at the appropriate emergency medical center.

In cases of massive over dosage, hydration and urinary alkalinization may be necessary to prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis have been shown to improve methotrexate elimination. However, effective clearance of methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer.

Patients who experience delayed early methotrexate elimination are likely to develop nonreversible oligouric renal failure. In addition to appropriate leucovorin therapy, these patients may require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micro-molar and the renal failure has resolved. If necessary, acute, intermittent hemodialysis with a high-flux dialyzer may also be beneficial in these patients.

#### 1.4.4.7 Pregnancy

Methotrexate is a known teratogenetic.

Adalimumab is Pregnancy Category B. An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (266 times human AUC when given 40 mg subcutaneous with MTX every week or 373 times human AUC when given 40 mg subcutaneous without MTX) and has revealed no evidence of harm to the fetuses due to adalimumab. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, adalimumab will not be used during pregnancy in this study.

It is not known whether adalimumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from adalimumab pregnant and/or lactating women will be excluded from this study.

Men must agree to avoid impregnating a woman while on this study.

Urine Pregnancy Test will be checked at screening, baseline, and monthly for methotrexate treated women through week 16, and at screening, baseline and at week 16 for adalimumab treated patients.

Men and women of childbearing potential will be required to practice adequate forms of contraception. Despite these measures, pregnancy may occur in female patients and in partners of male patients. Although pregnancy is not an SAE, the outcome of a pregnancy must be reported to detect a potential SAE, such as stillbirth or congenital anomaly. All pregnancies in female patients or partners of male patients treated with the study drug, which occur from the start of study drug administration and up to 30 days after dosing study drug, are reportable on a SAE form.

If a subject becomes pregnant while in the study, the study doctor will request permission to collect information about the pregnancy and information about the baby for up to 12 weeks after the baby is born. This follow-up will include telephone calls from a research team member (either doctor or nurse) to the subject approximately once every 3 weeks.

#### 1.4.4.8 Safety Plan

PPD (and CXR if indicated), and Hepatitis B and C will be checked at screening. Urine Pregnancy Test will be checked at screening, baseline, and monthly for methotrexate treated patients through week 16, and at screening, baseline and at week 16 for adalimumab treated patients. For adalimumab cohort: CBC, complete metabolic profile, CRP, and ANA will be checked at screening and 16 weeks after initiation of adalimumab. For methotrexate cohort: CBC, LFT, metabolic profile, and CRP will be checked at screening and at weeks 16 and 32. For methotrexate cohort: CBC, LFTs, lytes, BUN, and Cr will be checked after screening, then weekly until stable dose is reached, and then monthly until week 16. Vital signs and physical examination will be done at screening, baseline, and monthly. Adverse events assessment will be done at screening, baseline, and monthly. Skin biopsies will be done at baseline, week 1, week 2, week 4, and week 16. (**Appendix A**).

In the event that a subject experiences an adverse event, he/she will be promptly seen if possible or be seen by an emergency department physician. Costs for safety laboratory tests, as well as research visits, will be covered by the study sponsor. If emergency medical treatment or other needed medical care is required by subjects as a direct result of being in this research study, this treatment is available at the usual cost. Subjects or their insurance carriers will have to pay for any such emergency medical care. All needed facilities, emergency treatment, and professional services are available to subjects, just as they are to the general public. There are no plans to pay for subject's treatment if they get hurt or sick as part of this study. Tufts Medical Center has not set aside any money to pay for a research-related injury or illness, or medical expenses.

### 1.4.5 Compliance with Laws and Regulations

This study will be conducted in accordance with current U.S Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements.

## 1.5 MATERIALS AND METHODS

### 1.5.1 Subjects

#### 1.5.1.1 Subject Selection

Thirty (30) adult subjects with psoriasis will participate in the study. They will be recruited from Tufts Medical Center clinical population and from advertisement. Subjects who have provided informed consent will be screened using the following inclusion and exclusion criteria. (See **Appendix A**, the study flow chart, for screening assessments.)

#### 1.5.1.2 Inclusion Criteria

1. Adults 18 to 85 years of age with moderate to severe psoriasis, in general good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, and physical examination, and who are candidates for systemic or photo- therapy.
2. Presence of a psoriatic plaque of 2 cm or greater in an area which can be biopsied repeatedly.
3. Women are eligible to participate in the study if they meet one of the following criteria:
   A. Women of childbearing potential must undergo monthly pregnancy testing during the study and agree to use two of the following methods of contraception throughout the study and for 60 days after the last dose of study drug:
   - Oral contraceptives;
   - Transdermal contraceptives;
   - Injectable or implantable methods;
   - Intrauterine devices; and
   - Barrier methods (diaphragm with spermicide, condom with spermicide).

   Abstinence and Tubal Ligation are also considered a form of Birth control.

   B. Women who are postmenopausal (for at least one year), sterile, or hysterectomized.
4. Men must agree to avoid impregnating a woman while on this study.

#### 1.5.1.3 Exclusion Criteria

1. Patients <18 years old or >85 years old
2. Absence of a psoriatic plaque at least 2 cm in diameter
3. Active guttate, erythrodermic, or pustular psoriasis at the time of the screening visit
4. Evidence of skin conditions at the time of the screening visit (e.g. eczema) other than psoriasis that would interfere with evaluations of the effect of study medication on psoriasis
5. Inability to understand the consent process
6. Receipt of any investigational drugs or biologics within 4 weeks of study drug initiation
7. PUVA or oral systemic treatments within 4 weeks of study drug initiation.
8. Biologics within 3 months of study initiation
9. UVB therapy within 2 weeks of study drug initiation
10. Topical steroids, topical vitamin A or D analog preparations or anthralin within 2 weeks of study drug initiation. (Exception - topical steroids at no higher than moderate strength, are permitted on scalp, axillae, and groin but dose and formulation must be kept stable throughout trial.)
11. Methotrexate within 6 weeks of study initiation
12. History of prior treatment with adalimumab
13. History of primary non-response to methotrexate, infliximab or etanerecpt

14. History of prior discontinuation of methotrexate or a TNF antagonist for a safety-related reason that makes it unwise to restart either type of drug
15. Any internal malignancy within 5 years (fully excised cutaneous, basal cell carcinoma or squamous cell carcinoma are exceptions)
16. Pregnancy, not practicing effective birth control, or inability to practice safe sex during the length of the study
17. Lactation
18. Subjects who have known hypersensitivity to adalimumab or methotrexate or any of its components or who is known to have antibodies to etanercept
19. History of alcohol or drug abuse one year before and during the study.
20. Known HIV-positive status or any other immune-suppressing disease.
21. Presence of a grade 3 or 4 infection <30 days prior to the screening visit, between the screening visit and the first day of treatment on study, or any time during the study that in the opinion of the Investigator would preclude participation in the study.
22. Any grade 3 or 4 adverse event, or laboratory toxicity, at the time of the screening visit or at any time during the study, which in the opinion of the Investigator would, preclude participation in the study.

- Serum creatinine $\geq$ 3.0 mg/dL (265 micromoles/L)
- Serum potassium < 3.5 mmol/L or $\geq$ 5.5 mmol/L
- Serum ALT or AST $\geq$ 3 times the upper limit of normal for the Lab
- Platelet count < 100,000/$mm^3$
- WBC count < 3,000 cells/$mm^3$
- Hemoglobin, hematocrit, or red blood cell count outside 30% of the upper or lower limits of normal for the Lab

23. Receipt of live vaccines 1month prior to or while on study
24. A prior history of tuberculosis, and/or a positive PPD skin test/CXR at screening without appropriate treatment. Treatment of latent TB infections (for those with positive PPD tests) must be initiated prior to therapy with adalimumab or methotrexate.
25. Chronic hepatitis B or hepatitis C infection, history of multiple sclerosis, transverse myelitis, optic neuritis or epilepsy.

### 1.5.2 Method of Treatment Assignment

All consenting eligible subjects will receive active drug in an open-label study using adalimumab and methotrexate. There will be two cohorts, and randomization will be 1:1 adalimumab:methotrexate. Patients who are naive to both methotrexate and anti-TNF therapy will be equally distributed between methotrexate and adalimumab arms. Laboratory assessors are blinded to treatment and treatment outcome.

### 1.5.3 Study Treatment

Subjects will receive treatment on Days 1 and then weekly or every 2 weeks for 16 weeks. Subjects will have either injections or oral dosing, and will only receive treatment depending on their cohort.

For the injections, subjects will receive 80mg adalimumab (2 pre-filled syringes, each with 40mg) on day 1, and then 40mg on week 1 and then every 2 weeks (from week 1 through week 15). Dosing increase of injected drug is not permitted.

For oral dosing, patients will be dosed according to the CHAMPION study in single weekly doses of methotrexate: 7.5mg at week 0, increased to 10mg at week two, and increased to 15mg at week 4 for all patients. For oral dosing, if the PASI did not decrease by at least 50% at week 8, dosing will be increased to 20mg per week; the dose will be maintained at 15mg per week if the PASI decreased by 50% or more compared with baseline at week 8. If the PASI did not decrease by at least 50% at week 12, oral dosing will be increased to 25mg per week and will be maintained here; the oral dose will be maintained at 20mg per week if the PASI decreased by 50% or more compared with baseline at week 12.

All patients on methotrexate will also receive a dietary supplement of oral folate (5mg per week) beginning 48 hours after initiation of oral dosing and continued weekly thereafter on non-methotrexate dosing days.

### 1.5.3.1 Adalimumab Formulation

HUMIRA (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF). HUMIRA was created using phage display technology resulting in an antibody with human derived heavy and light chain variable regions and human IgG1:K constant regions. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. (FDA label 2008)

HUMIRA is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The drug product is supplied as either a single-use, prefilled pen (HUMIRA Pen) or as a single-dose, 1 mL prefilled glass syringe. Enclosed within the pen is a single-use, 1 mL prefilled glass syringe. The solution of HUMIRA is clear and colorless, with a pH of about 5.2. Each prefilled syringe delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of HUMIRA contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80, and Water for Injection, USP. Sodium hydroxide added as necessary to adjust pH. (FDA label 2008)

### 1.5.3.2 Methotrexate Formulation

Methotrexate (also known as MTX; N-(4-[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl)-L-glutamic acid; and amethopterin) is a folic acid analog and antagonist. It is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis. (FDA label 2008)

Each tablet contains methotrexate sodium in an amount equivalent to the labeled amount of methotrexate, and contains the following inactive ingredients: colloidal silicon dioxide, lactose (hydrous), magnesium stearate, microcrystalline cellulose, pregelatinized corn starch, sodium carbonate (monohydrate), sodium lauryl sulfate, sodium starch glycolate, and FD&C Red #40 Lake. The 5 mg also contains: D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake and FD&C yellow no. 6 aluminum lake. (FDA label 2008)

### 1.5.3.3 Dosage, Administration and Storage

#### a. Dosage

For the injections, subjects will receive 80mg adalimumab (2 pre-filled syringes, each with 40mg) on day 1, and then 40mg on week 1 and then every 2 weeks (from week 1 through week 15). Dosing increase of injected drug is not permitted.

For oral dosing, patients will be dosed according to the CHAMPION study in single weekly doses of methotrexate: 7.5mg at week 0, increased to 10mg at week two, and increased to 15mg at week 4 for all patients. For oral dosing, if the PASI did not decrease by at least 50% at week 8, dosing will be increased to 20mg per week; the dose will be maintained at 15mg per week if the PASI decreased by 50% or more at week 8. If the PASI did not decrease by at least 50% at week 12, oral dosing will be increased to 25mg per week and will be maintained here; the oral dose will be maintained at 20mg per week if the PASI decreased by 50% or more at week 12.

All patients on methotrexate will also receive a dietary supplement of oral folate (5mg per week) beginning after initiation of oral dosing. (See above for folic acid dosing.)

#### b. Administration

Research staff will administer drug and placebo injections on day 1 and train the subject to administer these. The research team members who will administer the drug and placebo include the principal investigator, a sub-investigator doctor, registered nurse (RN), or the licensed practical nurse (LPN). All of these team members have been professionally trained in administration of injections and have a thorough knowledge of the study, study drug, and placebo. They will monitor and evaluate the patient's condition during dosing and at study visits. Subjects will have subcutaneous injections in either the lateral arms, in their thighs, or in their abdomen. Patients will go home with pre-filled syringes for home injection and will go home with study drug for home administration.

#### c. Storage

Methotrexate is stored at 20° to 25°C (68° to 77°F) and it will be protected from light. It will be dispensed in tight, light-resistant containers.

Adalimumab must be refrigerated at 2-8° C (36-46° F). It cannot be Frozen, and the vial or/and pre-filled syringe will be protected from exposure to light. It will be stored in original carton until time of administration. It will go home with subjects in insulated bags with frozen packs.

### 1.5.3.4 Drug Compliance Assessment

Research staff will administer drug and placebo injections in clinic, and patients will administer oral dosing and injections at home. Dosing will be recorded in source documents.

### 1.5.4 Concomitant Therapy and Excluded Therapy

The following treatments are excluded during the study:

- Other systemic psoriasis therapies
- PUVA
- UVB

- Topical steroids, topical vitamin A or D analog preparations or anthralin within 2 weeks of study drug initiation. (Exception - topical steroids at no higher than moderate strength, are permitted on scalp, axillae, and groin but dose and formulation must be kept stable throughout trial.)
- Systemic corticosteroids
- Excessive alcohol consumption (drinking more than two drinks per day on average for men or more than one drink per day on average for women)

Subjects may continue to use any other prescription topical or systemic medications that they have been using on a regular basis. Alcohol use is discouraged. In addition, patients will be advised to contact their physician before treating themselves for cough, cold, sore throat, indigestion, diarrhea, or allergies.

### 1.5.5 Study Assessments

For a complete overview of the study assessments, see the flow chart in **Appendix A**.

#### 1.5.5.1 Screening Assessments (Visit 1, up to 4 weeks before baseline visit)

- Written informed consent and Research Authorization Form (to be signed)
- Demographics (including date of birth, sex and race)
- Review of inclusion and exclusion criteria
- Physical exam (including vital signs [pulse, blood pressure, respiratory rate, temperature], weight)
- Medical history
- Review of concomitant medications
- Target lesion scoring
- PASI, PGA, and BSA
- CBC, CMP, CRP, ANA, urinalysis, urine pregnancy test (if applicable)
- PPD
- CXR (if indicated)
- Hepatitis B and C

#### 1.5.5.2 Assessments during Treatments

Subjects will receive the following assessments:

**Week 0 (Visit 2, Baseline)**

- Randomization
- Review of inclusion and exclusion criteria
- Physical exam including vital signs (pulse, blood pressure, respiratory rate, temperature), weight,
- Review of concomitant medications
- Interim history/adverse event recording
- PASI, PGA, and BSA
- Target lesion scoring and photography
- Study drug administered
- Tissue Biopsy of Target Lesion (lesional and non-lesional)

**Weeks 1, 2, 4, 8, and 12 (Visits 3-7) For Adalimumab Cohort**

- Physical exam including vital signs (pulse, blood pressure, respiratory rate, temperature), weight,
- Review of concomitant medications
- Interim history/adverse event recording
- PASI, PGA, and BSA
- Target lesion scoring and photography
- Study drug administered (at week 1 only)
- Tissue Biopsy of Target Lesion (weeks 1, 2, and 4 only)
- Subjects will go home with study drug (at weeks 4, 8, and 12 only)

**Weeks 1, 2, 4, 8, and 12 (Visits 3-7) For Methotrexate Cohort**

- Physical exam including vital signs (pulse, blood pressure, respiratory rate, temperature), weight,
- Review of concomitant medications
- Interim history/adverse event recording
- PASI, PGA, and BSA
- Target lesion scoring and photography
- CBC, LFT, lytes, BUN, Cr, urine pregnancy test (if applicable, at weeks 4, 8, and 12 only)
- Study drug administered
- Tissue Biopsy of Target Lesion (weeks 1, 2, and 4 only)
- Subjects will go home with Methotrexate (at weeks 2, 4, 8, and 12 only)

**Week 16 (Visit 8, End of study & follow-up/Early termination)**

- Physical exam including vital signs (pulse, blood pressure, respiratory rate, temperature), weight,
- Review of concomitant medications
- Interim history/adverse event recording
- PASI, PGA, and BSA
- Target lesion scoring and photography
- CBC, CMP, CRP, ANA, urine pregnancy test (if applicable)
- Tissue Biopsy of Target Lesion
- For methotrexate-treated subjects: subjects will go home with adalimumab for 16 weeks

**Week 32 visit (for previous Methotrexate Cohort that then received Adalimumab)**

- This visit will be performed in General Dermatology Clinic by Dr. Gottlieb
- CBC, CMP

### 1.5.6 Subject Discontinuation

Subjects have a right to withdraw from the study at any time. If a subject is prematurely withdrawn from the study, the reason for study discontinuation will be recorded.

The subject may be withdrawn from the study for any of the following reasons:

- The subject or investigator determines that it is not in the subject's best interest to continue participation.
- The subject experiences a serious adverse event(s) or intercurrent illness that warrants the discharge of the subject.
- The subject's condition worsens

Tufts Medical Center may request the withdrawal of a subject because of protocol violations, administrative reasons, or any other valid and ethical reasons.

### 1.5.7 Study Discontinuation

This study may be terminated by Tufts Medical Center at any time.

### 1.5.8 Efficacy Measures

Tissue biopsy samples will be obtained at baseline (lesional and uninvolved skin) and at weeks 1, 2, 4, and 16 (lesional only) to assess biological markers.

#### 1.5.8.1 Immunohistochemistry

Tissue sections will be stained with haematoxylin (Fisher, Fair Lawn, New Jersey) and eosin (Shandon, Pittsburgh, Pennsylvania) (H&E) and with mouse anti-human monoclonal antibodies to Keratin 16 (Sigma Aldrich), CD3 (Becton Dickinson, San Jose, California), and CD11c (BD Pharmingen, San Diego, CA). A secondary biotin-labeled horse anti-mouse antibody (Vector Laboratories, Burlingame, California) will be amplified with the avidin-biotin complex (Vector Laboratories). 3-amino-9-ethylcarbazole (Sigma Aldrich) is the chromogen to be used. Epidermal thickness measures and cell counts (per 10X field) will be determined using computer-assisted image analysis (Image Pro-Plus (Media Cybernetics Co., Silver Spring, MD)). K16 keratin protein expression is quantitated on a 0-4 scale. Absence of suprabasal staining for K16 keratin is the normal pattern seen in normal or uninvolved skin and is assigned a score of "0". A total of 7 additional markers will be tested, including DC-LAMP, CD163, CD161, BDCA-1 and TRAIL. Other possible markers include, but are not restricted, to CD4, CD8, FOXP3, elastase and BDCA-2. Immunohistochemistry 10 histological markers will be studied, including K16, CD3, CD11c, DC-LAMP, CD163, CD161, BDCA-1, and TRAIL. Other possible markers, to be decided, include Langerin, CD4, CD8, FOXP3, elastase, and BDCA-2.

#### 1.5.8.2 Tissue mRNA gene expression

RNA will be extracted from skin biopsies frozen in liquid nitrogen using the RNeasy Mini Kit (Qiagen, Valencia, California). The primers and probes for TaqMan RT-PCR assays for IL-1, IL-6, IL-8. iNOS, p19 and p40 subunits of IL-23, IL-20, IFN-γ, IL-17A, IL-22, defensin-beta2, CCL-20, MX-1 and HARP will be generated using the Primer Express algorithm, version 1.0, using published genetic sequences (NCBI-PubMed).

All primers and probes are purchased from Applied Biosystems (Foster City, California). The RT-PCR reaction was performed using EZ PCR Core Reagents (Applied Biosystems). The samples are amplified and quantified on an Applied Biosystems PRISM 7700 using the following thermal cycler conditions: 2 min @ 50 °C; 30 min @ 60 °C; 5 min @ 95 °C; and 40 cycles of 15 sec @ 95 °C followed by 60 sec @ 60 °C. The human acidic ribosomal protein (HARP) gene, a housekeeping gene, is used to normalize each sample and each gene. HARP-

forward CGCTGCTGAACATGCTCAA, HARP-reverse TGTCGAACACCTGCTGGATG, HARP-probe 6-FAM-TCCCCCTTCTCCTTTGGGCTGG-TAMRA (Gene Bank Accession Number NM-001002). The data are analyzed by the software provided with the Applied Biosystems PRISM 7700 (Sequence Detection Systems, ver.1.7).

The directed analysis for RNA expression (above) targets genes which are likely to be regulated by a TNF inhibitor (adalimumab). Methotrexate might have a very different set of genes regulated. As such, a broad analysis of gene expression via a gene array may be the most informative and complementary to gene measures by real-time PCR. A number of inflammatory genes are not well detected on arrays, due to sensitivity, so good measures of T-cell cytokines and IL-23 are best done via RT-PCR. However, gene arrays do provide the broad overview that may be critical in finding different mechanisms of action of methotrexate vs. TNF inhibition. Gene arrays will be performed a small subset of patients depending on responses seen for (above) RNA expression.

### 1.5.9 Statistical Methods

#### 1.5.9.1 Analysis of the Conduct of the Study

There have been no studies which have measured relative in vivo effects of adalimumab compared with methotrexate in psoriasis patients and thus there are no existing data that can be used for designing a study with "classical" power calculations to estimate group sizes needed. Hence, to some extent, this is a pilot study to ascertain potential differences and the results of this study are needed to design future trials in which more formal power calculations can be done. Results from the CHAMPION study with adalimumab and methotrexate are used as a basis for determining significance and group size.

A two-arm comparison between adalimumab and methotrexate will be carried out. For power calculations, we assume that 80% of patients will suppress gene expression by 75% or more (defined by PASI 75) for adalimumab vs. only 36% for methotrexate (results from CHAMPION study, with 80% of adalimumab-treated patients achieving a PASI-75 after 16 weeks compared with only 36% of methotrexate treated patients). Assuming an $\alpha$ error of 0.05, the statistical power is 80% to detect a difference (at $p = 0.05$) with a one-way test (declaring the known polarity of the difference) and a group size of 15 per arm. By non-parametric statistics looking only for "improvement" with treatment, a group of 15 would tolerate 3 non-responders and yield significance.

The response score is a composite score made up of K16 immunohistochemistry staining, percent change in epidermal thickness, and percent change in K16 mRNA. The response score is generated by $\mu$-statistics. P-values for cell counts and gene expression changes are computed by Student's T-test. The patients' response scores are then correlated wit T cell, dendritic cell and inflammatory gene changes, which are ordered by $\mu$-scores.

#### 1.5.9.2 Baseline Demographics

The subject population will be representative of the demographic make-up of the greater Boston, MA area.

### 1.5.10 Data Quality Assurance

Accurate, consistent and reliable data will be ensured through the use of standard practices and procedures. Laboratory assessors are blinded to treatment and treatment outcome.

## 1.6 ASSESSMENT OF SAFETY

The safety of adalimumab and methotrexate will be assessed through collection and analyses of protocol defined adverse events. The treating physicians will assess for all serious adverse events (SAEs) that occur during treatment until the end of the study.

### 1.6.1 Adverse Events and Reporting Definitions

In the event of an adverse event, the first concern will be for the safety of the subject. The investigator will report to the IRB any serious adverse event (whether expected or unexpected), which is assessed by the investigator to be reasonably or possibly related to study drug. All events meeting these criteria will be reported for the time period beginning with exposure to study drug (Baseline visit) through the end of the assessment period (16 weeks). Serious criteria, definitions, and guidance for reporting are as follows.

An adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, current illness, abnormal laboratory finding) that emerges during study drug treatment or is a pre-existing condition that worsens relative to the pretreatment state, regardless of the suspected cause.

Serious adverse events (SAE) are adverse events occurring at any dose which meet one or more of the following serious criteria:

- It resulted in **death** (i.e., the adverse event caused or led to death)
- It was **life-threatening** (i.e., the adverse event placed the subject at immediate risk of death; it does not apply to an adverse event that hypothetically might have caused death if it were more severe)
- It required or prolonged inpatient **hospitalization** (i.e., the adverse event required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not serious adverse events by this criteria)
- It was **disabling** (i.e., the adverse event resulted in a substantial disruption of the subject's ability to carry out normal life functions)
- Is a congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the trial drug prior to conception or during pregnancy)
- It does not meet the above criteria but **may jeopardize the subject** or **may require medical or surgical intervention** to prevent the outcomes listed above.

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (PI). Unexpected adverse events are those not listed in the PI or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the PI.

Adverse events that are attributable to study drug and ongoing at end of study will be followed to

resolution or stability.

### 1.6.2 Methods for Eliciting, Recording and Assessing Adverse Events

#### 1.6.2.1 Eliciting Adverse Events

To elicit subject reporting of adverse events, simple questions with minimal connotations will be used as the initial questions at all evaluation points during the study. For example:

- How have you felt since your last visit?
- Have you had any health problems since you were last here?
- Have you had any unusual or unexpected worsening of your underlying medical condition?

#### 1.6.2.2 Recording Adverse Events

The Investigators will consider the following when assigning a primary event term:

- Whenever possible, recognized medical terms will be used when recording adverse events. Colloquialisms and/or abbreviations will be avoided.
- If known, the diagnosis will be recorded (i.e. disease) rather than component signs and symptoms. However, signs and symptoms that are considered unrelated to an encountered syndrome or disease will be recorded as individual adverse events.
- Adverse events occurring secondary to other events (e.g., sequelae) will be identified by the primary cause. A "primary" adverse event, if clearly identifiable, generally represents the most accurate clinical term to record. Events occurring secondary to the primary event will be described in the narrative description of the case. For example:

| | | | | | | |
|---|---|---|---|---|---|---|
| orthostatic hypotension | → | fainting and fall to floor | → | head trauma | → | neck pain |

#### 1.6.2.3 Assessing Causality (Relationship of Study Drug to Adverse Event):

The investigator will determine which adverse events are associated with the use of the trial drug.

**For reporting purposes, an AE will be regarded as possibly or probably related to the use of the investigational product if the investigator believes:**

- There is a clinically plausible time sequence between the onset of the AE and study drug administration; and/or
- There is a biologically plausible mechanism for study drug causing or contributing to the adverse event; and/or
- The adverse event cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.

**For reporting purposes, an AE will be regarded as probably not related to the use of the investigational product if the investigator believes:**

- Another cause of the adverse event is most plausible; and/or
- A clinically plausible temporal sequence is inconsistent with the onset of the adverse event and study drug administration; and/or
- A causal relationship is considered biologically implausible.

### 1.6.3 Reporting of Serious Adverse Events

#### 1.6.3.1 General Reporting of Serious Adverse Events Associated with Study drug

All SAEs that are serious and reasonably or probably related to study drug (this applies to both expected and unexpected events) will be recorded and reported to the IRB within five (5) days. The address is:

Institutional Review Board
Tufts Medical Center
Tufts University Health Sciences
35 Kneeland Street
8th Floor, Box 817
Boston, MA 02111
Phone (617) 636-7512
Fax (617) 636-8394

If the SAE is fatal or life threatening AND associated with the use of study drug, the FDA will be notified by telephone or fax within 7 calendar days. The IRB will be notified by telephone immediately, and a formal adverse event report will follow within 5 days.

The Principal Investigator will prepare IND Safety Reports using FDA Medwatch Form 3500A with supporting documents. A copy of all FDA submitted reports will be faxed to Immune Control (610-567-2045) within 24 hours of submittal to the FDA.

## 1.7 INVESTIGATOR REQUIREMENTS

### 1.7.1 Study Completion

The following data and materials are required by Tufts Medical Center before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period (if applicable)
- Case Report Forms properly completed by appropriate study personnel and signed and dated by the investigator (if applicable)
- Copies of protocol amendments and IRB approval/notification (if applicable)
- A summary of the study prepared by the Principal Investigator (will accept IRB summary close letter) (if applicable)
- All regulatory documents (e.g., curricula vitae for each Principal Investigator, U.S. FDA Form 1572)

### 1.7.2 Study Drug Accountability

The Investigator is responsible for the control and distribution of study drug. All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure.

### 1.7.3 Disclosure of Data

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study will be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, and the IRB/EC.

### 1.7.4 Retention of Records

All records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, will be retained by the Principal Investigator for 2 years after the investigation is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

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## 1.9 APPENDICES

### 1.9.1 Appendix A: Study flow chart

| Item | Screen (visit 1) | Baseline Week 0 (visit 2) | Week 1 (visit 3) | Week 2 (visit 4) | Week 4 (visit 5) | Week 8 (visit 6) | Week 12 (visit 7) | Week 16 (end of study follow-up/early term) (visit 8) |
|---|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | | |
| Collection of demographic information | X | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | |
| Medical history | X | | | | | | | |
| Physical exam (incl. vital signs, weight) | X | X | X | X | X | X | X | X |
| PPD, CXR[2] | X | | | | | | | |
| Dermatologic evaluations (target lesion score and photography, PASI, PGA, BSA) | X | X | X | X | X | X | X | X |
| Target lesion Biopsy | | X[3] | X | X | X | | | X |
| Concomitant meds review | X | X | X | X | X | X | X | X |
| Adverse event recording/interim history | X | X | X | X | X | X | X | X |
| Study drugs administered | | X | X | X | X | X | X | X |
| CBC, CMP, urine pregnancy test (if applicable) | X | | X[1,4] | X[1,4] | X[1] | X[1] | X[1] | X[1] |
| CRP, ANA | X | | | | | | | X |

[1]CBC, CMP and Urine Pregnancy test (if applicable) only for MTX-treated subjects
[2]CXR will only be performed if necessary at screening
[3]Biopsy at Baseline will be for lesional and non-lesional skin
[4]Urine Pregnancy (if applicable) not performed at week 1 or week 2

### 1.9.2 Appendix B: Target Lesion Scoring for psoriasis

**TARGET LESION SCORING:** Write score for erythema, scaling, and thickness below (scale of 0 to 4 for each of the three parameters). The 3 scores will then be summed.

| | | 0.5 * | 1.5 * | 2.5 * | 3.5 * |
|---|---|---|---|---|---|
| Signs | 0 | 1 | 2 | 3 | 4 |
| **Scaling (S)** | None | **Mild**: Mainly fine (powdery) scales; some lesions at least partially covered | **Moderate**: Somewhat coarser scales (thin flakes); most lesions at least partially covered | **Severe**: Coarse, thick scales virtually all lesions covered; rough surface | **Very severe**: Coarse, very thick scales; all lesions covered; very rough surface |
| **Erythema (E)** | **None** | **Mild**: Light red coloration (barely detectable) | **Moderate**: Definite red coloration | **Severe**: Very red coloration | **Very Severe**: Extreme red coloration typical of untreated psoriatic plaque |
| **Induration (I) or Plaque elevation** | **None** | **Mild**: Slight but definite elevation above normal skin level | **Moderate**: Easily palpable elevation with rounded or sloped edges to plaque | **Severe**: Definitely elevated lesions with hard sharp edges to plaque | **Very Severe**: Elevation with very hard sharp edges to plaque |

*Intermediate grades (0.5, 1.5, 2.5, and 3.5) are mid points between the defined grades (0, 1, 2, 3, and 4)

**LESION LOCATION: _____**

**S + E + I = Total score**

_____ + _____ + _____ = _____**Total score**
(S) (E) (I)

_____(Assessor's Signature) _____Date

### 1.9.3 Appendix C: Psoriasis Area and Severity Index (PASI)

**Psoriasis Area and Severity Index:** Write score for erythema, scaling, and thickness below (scale of 0 to 4 for each of the three parameters). The 3 scores will then be summed and will be multiplied with the numerical value of the area affected and with the various percentages of the four body area. These values will then be added together for Total PASI score.

| Row | | Head | Upper Limbs | Trunk | Lower Limbs |
|---|---|---|---|---|---|
| **1** | **Scaling[1]** | | | | |
| **2** | **Erythema[1]** | | | | |
| **3** | **Induration or thickness[1]** | | | | |
| **4** | **Total Each Column** | | | | |
| **5** | **Degree of Involvement[2]** | | | | |
| **6** | **Multiply Row 4 by Row 5** | | | | |
| **7** | **Weighted multiplier** | **X 0.10** | **X 0.20** | **X 0.30** | **X 0.40** |
| **8** | **Multiply Row 6 by Row 7** | | | | |
| **9** | **Total PASI (add together each column from Row 8)** | | | | |

[1] Rank of scale, erythema, and induration a 0–4 scale: 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe

[2] Degree of psoriatic involvement based on a percentage for skin covered with psoriasis for each area: 0 = none, 1 = <10%, 2 = 10 to < 30%, 3 = 30 to <50%, 4 = 50 to <70%, 5 = 70 to <90%, 6 = 90 to 100%

_____(Assessor's Signature) _____Date

### 1.9.4 Appendix D: Physician's Global Assessment (PGA) and Body Surface Area (BSA)

**Physician's Global Assessment:** Assign an overall score for erythema, scaling, and thickness below (scale of 0 to 5 for each of the three parameters).

| Score | Category | Category Description |
|---|---|---|
| **0** | Clear | Induration = none<br>Erythema = none or faint pink, hyperpigmentation<br>Scale = none |
| **1** | Minimal | Induration = possible, difficult to ascertain slight elevation<br>Erythema = up to moderate (up to moderate red coloration)<br>Scale = minimal; occasional fine scale |
| **2** | Mild | Induration = mild (slight but definite elevation)<br>Erythema = up to moderate (up to moderate red coloration)<br>Scale = mild / fine (partially or mostly covering lesions) |
| **3** | Moderate | Induration = moderate (rough or sloped edges of lesions)<br>Erythema = moderate (definite red coloration)<br>Scale = moderate; coarser predominated |
| **4** | Severe | Induration = marked (hard or sharp edges)<br>Erythema = bright red coloration<br>Scale = marked; coarse, thick, non-tenacious predominates |
| **5** | Very Severe | Induration = very marked (hard or sharp edges)<br>Erythema = deep red coloration (dusky)<br>Scale = very severe; very coarse, thick and tenacious scale |

Body Surface Area (BSA) with psoriasis_____%

_____(Assessor's Signature) _____Date

## 1.10 PROTOCOL SIGNATURE PAGE

**Principal Investigator:**

| Signature of Investigator | Date |
|---|---|
| Printed Name of Investigator | |

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, instructions from Abbott representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.