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**GENERIC DRUG NAME / COMPOUND NUMBER:** Apratastat / TMI-005

**PROTOCOL NO.:** 3140A1-200-WW

**PROTOCOL TITLE:** A Double-Blind, Placebo-Controlled, Parallel, Randomized Study to Evaluate the Efficacy and Safety of 3 Oral Dose Levels of TMI-005 in Subjects With Active Rheumatoid Arthritis on a Background of Methotrexate

**Study Centers:** An unknown number of study centers in the United States and Canada took part in the study and randomized subjects.

**Study Initiation and Final Completion Dates:** Data not available for study initiation date. The final completion date was August 2005.

**Phase of Development:** Phase 2

**Study Objectives:**

Primary Objective: To compare the efficacy and the safety of 3 dose levels of oral TMI-005 (apratastat), in comparison with placebo in subjects with active rheumatoid arthritis (RA) who had been receiving stable doses of methotrexate (MTX).

Secondary Objectives:

- To compare the efficacy and the safety of apratastat among 3 dose levels.
- To assess health outcomes measures.
- To assess American College of Rheumatology (ACR) 20, ACR 50, and ACR 70 responses at all time points and the components of ACR response criteria.
- To assess disease activity score-28 (DAS-28).
- To assess other measures of disease activity.
- To assess population pharmacokinetics of apratastat.
- To search for biomarkers that correlate with severity of RA and/or clinical response to apratastat using peripheral blood mononuclear cells gene expression and, possibly, protein expression profiling in a subset of subjects at selected sites.

## METHODS

### Study Design:

This was a double-blind, placebo-controlled, parallel, randomized, multicenter, outpatient, comparative study in subjects with active RA who have had an inadequate response to stable dose of MTX (7.5–20 mg once weekly). The study consisted of up to a 4-week screening period, a 12-week double-blind treatment period and a follow-up period of approximately 1 to 2 weeks after the last dose of study drug administration. Each subject participated for up to 18 weeks. At Baseline, subjects who met all eligibility criteria were randomly assigned to 1 of 4 groups: 3 dose levels of apratastat or placebo. The use of placebo as a control was necessary to provide a quantitative assessment of drug effect. Subjects continued taking their same weekly dose of MTX as concomitant therapy throughout the study. The schedule of activities is presented in Table 1.

## Table 1. Schedule of Activities

| Study Period | Screen | BL | Treatment | | | | Follow-Up | Post-Study |
|---|---|---|---|---|---|---|---|---|
| **Study Scheduled Visit** | **SCR** | **Baseline** | **Postdose** | **Week 2, 4, 8** | **Week 12** | **Early Termination** | **Final Study Visit** | **Post-Study[a]** |
| **Study Week** | **-1 to -4** | **Day 1** | | **2[b], 4[b], 8[b]** | **12[b]** | | **13 - 14[c]** | |
| Informed consent | X | | | | | | | |
| Review eligibility criteria | X | X | | | | | | |
| Medical history | X | | | | | | | |
| ACR classification of functional status | X | | | | | | | |
| DMARD/RA treatment history | | X | | | | | | |
| Physical examination | X | X | | X | X | X | X | X[a] |
| Height and weight[d] | X | | | | | | | |
| Vital signs[e] | X | X | | X | X | X | X | X[a] |
| Joint assessment (28-joint count)[f] | X | X[f] | | X | X | X | | |
| Abduction of shoulders | X | X | | X | X | X | X | X |
| Hands and feet radiographs[g] | X | | | | | | | |
| ECG (12-lead) | X | X | | | X | X | | |
| Chest radiograph (PA and lateral) [g] | X | | | | | | | |
| Prior medication/treatment for conditions other than RA (past 30 days) | | →X | | | | | | |
| Concomitant medication/treatment | | | | X→ | X→ | X | X | X[a] |
| Laboratory evaluations[h] | X | X | | X | X | X | X | X[a] |
| β-HCG[i] | X | X | | X[i] | X | X | X | |
| Rheumatoid factor | X | | | | X | X | | |
| CRP | X | X | | X | X | X | | |
| ESR | X | X | | X | X | X | | |
| Hepatitis B surface antigen | X | | | | | | | |
| Hepatitis C antibody[j] | X[j] | | | | | | | |
| PK blood sample collection at selected sites [k] | | X | | X | X | | | |
| Pharmacogenomic sample collection at selected sites [l, m] | | X[m] | | X[m] | X[m] | | | |
| Study termination[n] | | | | | | | X | |
| Physician global assessments | X | X | | X | X | X | | |
| Patient global assessments | X | X | | X | X | X | | |
| Morning stiffness duration | X | X | | X | X | X | | |
| Pain VAS | X | X | | X | X | X | | |

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| Patient general health VAS[f] | X | X[f] | | X | X | X | | |
| HAQ[f] | | X[f] | | X | X | X | | |
| Fatigue VAS[f] | | X[f] | | X | X | X | | |
| Dispense TA[o] | | | X | X | | | | |
| Administer TA[o] | | | X→ | → | X | | | |
| Dispense TA recording worksheet[p] | | | | X | | | | |
| TA capsule count/calculate compliance | | | | X | X | X | | |
| Adverse event recording[q] | X | → | → | → | → | → | X | X[a] |

β-HCG = beta-human chorionic gonadotropin; AEs = adverse events; ACR = American College of Rheumatology; BL = Baseline; CRF = case report form; CRP = C-reactive protein; DMARD = Disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; ECG = electrocardiogram; HAQ = health assessment questionnaire; HCV-RIBA = hepatitis C virus recombinant immunoblot assay; PA = posteroanterior; PK = pharmacokinetics; RA = rheumatoid arthritis; SCR = screening; TA = test article; VAS = visual analog scale.

a. Evaluation performed to follow up AEs, or any abnormal laboratory or physical findings at the final visit or those that occurred within 7 days after the last dose of study drug if an early withdrawal.
b. Study Weeks 2 to 12 visits occurred within ± 3-day window of the appropriate date.
c. The Follow-Up (Final) Visit was to be completed by all subjects, regardless of whether they had completed 12 weeks of study drug treatment. This visit occurred at Study Week 13 –14 for subjects who had completed 12 weeks of study drug treatment. Subjects that were withdrawn early from the study had to complete this visit 1-2 weeks after their early termination visit.
d. Height at Screening. Body weight at Screening.
e. Vital signs: blood pressure, pulse rate, respiratory rate, and oral or tympanic temperature (°F or °C) after sitting for 5 minutes.
f. Waived if Baseline visit occurred within 7 days of Screening.
g. Hands and feet radiographs were performed at Screening, if needed, for diagnostic purpose of RA; chest radiograph were to be performed at Screening unless a historical radiograph was available within 1 month.
h. Laboratory evaluations (ie, hematology, chemistry, urinalysis, coagulation tests).
i. Serum β-HCG pregnancy test was completed for women aged <60 years, except those who were surgically sterile by a documented hysterectomy, bilateral oophorectomy, or were postmenopausal. This test was not done at the Week 2 visit.
j. If Hepatitis C Antibody was positive, a HCV-RIBA test had to be completed for confirmation.
k. Day 1: within 3 hours predose, Week 4 visit: within 3 hours predose, between 0.5 and 2 hours postdose, Week 8 visit: within 3 hours predose, between 2 and 4 hours postdose, Week 12 visit: within 3 hours predose, between 4 and 8 hours postdose. Population PK samples were not collected at Week 2.
l. Subjects had to sign and date a special consent form for pharmacogenomic testing before any pharmacogenomic blood samples were drawn.
m. At selected sites, pharmacogenomic blood samples (whole blood) were collected on Day 1 (before starting treatment), Week 2, and Week 12 (or final visit in case of early withdrawal).
n. Study termination CRF record was completed at the conclusion of the Follow-Up Visit.
o. Study drug had to be administered 3 times daily, approximately 8 hours between each dose.
p. Subjects who participated in PK blood sampling, subjects had recorded the dosing date and time for the last 3 doses before the day of the Weeks 4, 8 and 12 visits on the

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TA recording worksheets and bring them to study site at the respective visits.

q. To be collected for the entire duration of the study and followed post-study if the event continued.

**Number of Subjects (Planned and Analyzed):** A total of 360 subjects were planned to be randomized with 90 subjects in each group. Data not available for the total number of subjects randomized.

**Diagnosis and Main Criteria for Inclusion and Exclusion:** The study included male and female subjects aged 18 to 75 years, who met ACR criteria for RA; had active RA; had disease duration of at least 6 months and also had disease onset at >16 years of age.

Main Exclusion Criteria: Subjects who had any prior use of anti-tumor necrosis factor α biologics, rituximab, receipt of anti-CD4 or diphtheria interleukin-2 fusion protein or other immunosuppressive biologics (except for anakinra); who were largely or wholly incapacitated with the subject bedridden or confined to a wheelchair, permitting limited or no self-care; and pregnant or breastfeeding women or women planning to become pregnant during the study or within 12 weeks after the last dose of study drug were excluded from the study.

**Study Treatment:** Study drug was provided as capsules containing 50 mg, 100 mg, and 150 mg apratastat or a matching placebo. Eligible subjects in each treatment group received the double-blind study drug as an oral daily morning, mid-afternoon and evening dose of either 50 mg apratastat, 100 mg apratastat, 150 mg apratastat or placebo. The duration of study treatment was 12 weeks.

**Efficacy Endpoints:**

Primary Endpoint:

- ACR 20 response rate at Week 12.

Secondary Endpoints:

- ACR 20 response rate at Weeks 2, 4 and 8.
- ACR 50 and ACR 70 response rate.
- Total number of painful joints.
- Total number of swollen joints.
- DAS-28 score.
- Duration of morning stiffness.
- Physician Global Assessment of Disease Activity.
- Patient Global Assessment of Disease Activity.
- Pain visual analog scale (VAS).
- Erythrocyte sedimentation rate (ESR).

- C-reactive protein (CRP).
- Patient general health VAS.
- Health assessment questionnaire (HAQ).
- Fatigue VAS.

**Safety Evaluations:** Safety evaluations included recording of adverse events (AEs), physical examinations, evaluation of shoulder abduction, body weight measurements, elicited history reported by the subjects, vital sign measurements, 12-lead electrocardiograms, posteroanterior and lateral chest radiographs, and clinical laboratory evaluations.

**Statistical Methods:**

The intent-to-treat population was defined as all randomized subjects.

The modified intent-to-treat (mITT) population was defined as all randomized subjects who received at least 1 dose of test article. The mITT was the primary population for efficacy analysis and safety analysis.

The per-protocol population was a subset of mITT population excluding subjects who had major protocol violations.

Statistical comparison of the treatment groups was conducted for demographic and baseline characteristics. One-way analysis of variance models with treatment group as a factor were used to compare groups for all variables except nominal attributes (eg, sex), which were compared by Fisher's exact test.

The primary endpoint was subject ACR 20 responses at Week 12. The comparisons of primary interest were each apratastat dose level versus placebo. A logistic regression model with treatment as a factor was used. Subjects who discontinued therapy before the end of Week 12 or for whom data were insufficient to assess ACR 20 response at Week 12 were classified as non-responders for the primary analysis. The observed cases analysis was also employed.

For the comparisons of the 3 doses to placebo, Hochberg's step-up approach was used to adjust for multiple comparisons. At the first step, if the least significant comparison (highest p-value) to placebo was significant at the 0.05 level, all 3 groups were declared significantly different from placebo. If the least significant comparison was not significant at the 0.05 level, the second least significant result was compared to placebo at the 0.025 level. If this was significant both that and the remaining group were declared significantly different from placebo. Finally, if significance was not reached in the first 2 steps, the remaining group was compared to placebo at the 0.0167 level.

For the secondary endpoints, the ACR response rates were analyzed in the same way as the primary endpoint. Subjects who discontinued therapy before the end of Week 4 (8 or 12, respectively) or for whom data were insufficient to assess ACR response at Week 4 (8 or 12,

respectively) were classified as non-responders for this analysis at the specific week. The observed cases analysis was also employed. Change from baseline for continuous and ordered secondary variables were analyzed using an analysis of covariance (ANCOVA) with treatment as a factor and baseline as a covariate, followed by all the pairwise comparisons of the groups. If the assumptions of normality were violated, then an ANCOVA on ranked data was performed, with treatment as a factor, and ranked baseline as a covariate. For those variables, the last observation carried forward approach and an observed cases analysis was used.

The incidence of all AEs, treatment-emergent AEs, potentially clinically important laboratory measurements, and premature discontinuations during the study were compared between treatment groups using Fisher exact test procedures. When statistically significant overall differences among groups were found, pairwise comparisons between treatment groups were performed. Changes in laboratory means, body weight, and vital signs were compared among treatment groups by ANCOVA.

**RESULTS**

**Subject Disposition and Demography:** Data not available.

**Efficacy Results:** Data not available.

**Safety Results:** Data not available.

**CONCLUSIONS:** No study conclusions were available.