2. SYNOPSIS

Name of Sponsor/Company: Chelsea Therapeutics, Inc	**Individual Study Table Referring to Part of the Dossier** Volume: Page:	***(For National Authority Use Only)***
Name of Finished Product: CH-4051		
Name of Active Ingredient: CH-4051		

Title of study: A Phase II, Multi-center, Randomized, Parallel-Group, Double-blind, Methotrexate-controlled Study to Assess the Clinical Efficacy, Safety, and Tolerability of CH-4051 in Patients with Active Rheumatoid Arthritis Who Have Shown an Inadequate Response to Methotrexate Monotherapy

Principal investigator: Arthur Kavanaugh, MD

Study centers: This was a multi-center, multi-national study conducted in Argentina, Bulgaria, Czech Republic, Mexico, Poland, and the United States. Approximately 75 centers were planned, 67 centers were activated to screen patients, 55 centers screened at least 1 patient, and 50 centers enrolled at least 1 patient.

Publication(s): None

Study period: 13 September 2010 to 26 March 2012	**Phase of development:** 2

Objectives:

Primary objective:

- Demonstrate clinical efficacy of 1 or more doses of CH-4051 (0.3 mg, 1.0 mg, 3.0 mg, and 3.0 mg with 1.0 mg folic acid supplementation orally [p.o.] daily) compared to MTX (20 mg/week) with 1.0 mg of folic acid supplementation p.o. daily as measured by the hybrid American College of Rheumatology (hACR) classification score, followed in a hierarchical step-down analysis of the proportion of patients achieving ACR20.

Secondary objectives:

- Assess the clinical efficacy of CH-4051 using Disease Activity Score (DAS)28 scores;
- Assess the clinical efficacy of CH-4051 through analyses of the area under the curve (AUC) of the hACR and DAS28 scores;
- Proportion of patients achieving ACR50 and ACR70 response;
- Assess the clinical efficacy of CH-4051 through analyses of the AUC of the ACR20, ACR50, and ACR70;
- Assess linear trends in the hACR, DAS28, and ACR20 scores across dose groups;
- Assess the clinical efficacy of CH-4051 using European League Against Rheumatism (EULAR) “good” and “moderate” response criteria;
- Assess the clinical efficacy of CH-4051 using mean changes from Baseline in the

components of the ACR and DAS28 response criteria;

- Assess the clinical efficacy of CH-4051 using mean change from Baseline of morning stiffness;
- Evaluate the safety and tolerability of CH-4051 in rheumatoid arthritis (RA) patients as determined by the frequency and severity of adverse events (AEs), laboratory abnormalities, and dropouts due to AEs.

Methodology: Multi-center, multi-national, double-blind, randomized, active-controlled (methotrexate [MTX]), 3-month study with 4 dosages of CH-4051 (0.3 mg, 1.0 mg, 3.0 mg, and 3.0 mg with 1.0 mg of folic acid supplementation p.o. daily) compared to a "standard" dose of MTX at 20 mg per week with 1.0 mg of folic acid supplementation p.o. daily. The study population must have been diagnosed with RA per ACR criteria and met all of the inclusion criteria and none of the exclusion criteria. Patients must have otherwise been in good general health. As CH-4051 is a potent antifolate, to ensure the highest level of patient safety, this study was conducted in 2 parts:

Part A: Patients were randomized to 0.3 mg CH-4051, 1.0 mg CH-4051, or MTX with 1.0 mg of folic acid supplementation in a 2:2:1 ratio.

Part B: Patients were not randomized into Part B until the Data Monitoring Committee (DMC) reviewed safety data from Part A when approximately 25 patients (10 patients in each CH-4051 dose group and 5 patients in the MTX group) completed 3 months of treatment. At this time the DMC made a recommendation to commence randomization to 3.0 mg CH-4051, 3.0 mg CH 4051 with 1.0 mg of folic acid, or MTX in a 2:2:1 ratio. This randomization resulted in a 1:1:1:1:1 treatment ratio at the end of randomization. No stratification at randomization occurred.

Number of patients (planned and analyzed): Up to 250 patients were planned with the intent that approximately 215 patients (43 per treatment arm) would complete the 12-week treatment period. A total of 250 patients were randomized, 249 patient received study treatment, and 198 patients completed the 12-week treatment period.

Diagnosis and main criteria for inclusion:

1. Patients must have been between the ages of 18 and 80;
2. Had diagnosed active RA according to ACR criteria functional class I-III;
3. Had at least 6 swollen joints (max = 66) and 6 tender joints (max = 68) at screening and baseline visits;
4. Patients must have had at least one of the following:
    a. C-reactive protein $\geq$ 1.0 mg/dl at Screening;
    b. Erythrocyte sedimentation rate $\geq$ 28 mm/hour;
5. Patients must have been taking MTX between 15 mg/week and 25 mg/week for at least 3 months and at a stable dose for at least 6 weeks;
6. Patients must have been either rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) positive;
    a. Patients who were not RF or anti-CCP positive may have been entered into the study only after consultation with and approval by the medical monitor
7. Patients must have voluntarily signed the informed consent.

Test product, dose and mode of administration, batch number:

CH-4051 0.3 mg capsules, p.o.: Batch numbers 339858

CH-4051 1.0 mg capsules, p.o: Batch numbers 339471

CH-4051 3.0 mg capsules, p.o.: Batch numbers 338972

CH-4051 placebo capsules, p.o.: Batch numbers 338725

Folic acid 1.0 mg capsules, p.o.: Batch numbers 339996

Folic acid placebo, capsules, p.o.: Batch numbers 338725

Duration of treatment: A maximum of 20 weeks (up to 2 weeks screening, followed by a 2 week washout period, followed by a 12-week randomized treatment period, followed by a 4-week follow-up).

Reference therapy, dose and mode of administration, batch number:

Methotrexate, 20 mg capsules, p.o.: Batch numbers 341339

Methotrexate placebo capsules, p.o.: Batch numbers 338725

Folic acid 1.0 mg capsules, p.o.: Batch numbers 339996

Folic acid placebo, capsules, p.o.: Batch numbers 338725

Criteria for evaluation:

Primary efficacy: Co-primary efficacy parameters included hACR and ACR20 at Week 12.

Secondary efficacy: Secondary efficacy parameters included hACR at each postbaseline visit, AUC for hACR from Week 2 to Week 12, ACR component scores (number of tender joints and number of swollen joints, patient global assessment of disease activity measured by visual analogue scale [VAS], patient assessment of pain [VAS], health assessment questionnaire disability index [HAQ_D1], C-reactive protein, and erythrocyte sedimentation rate at each visit), ACR20/50/70 assessment at each postbaseline visit, DAS28 at each postbaseline visit, AUC change from Baseline for DAS28 from Week 2 to Week 12, EULAR response categories for DAS28, and morning stiffness.

Safety: Adverse events, laboratory evaluations (hematology, chemistry, urinalysis, liver function tests), vital signs, physical examination, and medical history.

Statistical methods:

This Phase II proof-of-concept trial was designed to provide evidence of the efficacy of 4 dosages of CH-4051 (0.3 mg, 1.0 mg, 3.0 mg, and 3.0 mg with 1.0 mg folic acid supplementation p.o. daily) as compared with MTX at 20 mg/week. The dose-response of CH-4051 was also to be characterized to provide guidance for the next research goals.

The effect of folic acid on CH-4051 has yet to be determined. Therefore any dose-dependency assessments with the 3.0 mg CH-4051 group and the 3.0 mg CH-4051 with 1.0 mg folic acid supplementation were to be combined where appropriate. The 2 groups were combined for the primary efficacy analyses only; the groups are also reported separately.

The results were to be considered hypothesis generating rather than confirmatory; the alpha was set at 0.05 two-tailed to aid in decision-making. The data was to be summarized as mean values and the traditional 95% confidence intervals to aid in the interpretation of the clinical relevance of differences in comparative treatment response among the 4 CH-4051 groups. The efficacy was to be combined with the safety profile of each group for final decision-making.

Per agreement with Chelsea, the gate-keeping strategy for testing of the co-primary endpoints described in Section 12.6.1.1 of the protocol was not used for the primary efficacy analysis. *P*-values for the ACR20 at Week 12 are presented regardless of the statistical significance of the hACR analysis. It was anticipated that 1 interim analysis would be performed. As the purpose of the interim analysis was not to stop the study for superior efficacy, the conservative Hybittle/Peto alpha spending approach was used. At the interim analysis, an alpha level of 0.001 was used for both the analysis of hACR and ACR20. The final analysis of the co-primary endpoints used an alpha level of 0.049.

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SUMMARY—RESULTS:

Efficacy results:

Primary Efficacy Endpoints:

The co-primary efficacy variables were the change in the mean hACR score from Baseline to Week 12 and the proportion of patients achieving an ACR20 response at Week 12.

In the mITT population, CH-4051 groups demonstrated evidence of efficacy as measured by the change in the hACR. There was a dose response observed at Week 12 in the CH-4051 groups, with increasing efficacy from 0.3 mg/day (15.0%) to 1.0 mg/day (17.2%) to 3.0 mg/day (25.5%). There was no evidence that the addition of folic acid to the CH-4051 3.0 mg/day treatment decreased the efficacy of CH-4051 (25.5% with CH-4051 alone vs 25.4% with CH-4051 + FA). The highest mean hACR response was seen in the MTX group (38.4%). The difference in the hACR of MTX vs CH-4051 was statistically significant ($p<0.05$) in all groups except for 3.0 mg/day + FA. Interestingly, while the hACR scores declined in the MTX group at Week 16, the scores in the CH-4051 groups continued to improve.

For the ACR20 at Week 12, all groups showed marked responses with >40% of patients having an ACR20 response. However a dose response was not apparent in the CH-4051 groups. The MTX group had the highest proportion of patients with an ACR20 response (56.0%), but this difference was not statistically significant compared to the CH-4051 groups, except for the CH-4051 3.0 mg/day group ($p=0.03$). As with the hACR, the percent of ACR20 responders declined at Week 16 in the MTX group, but generally continued to increase in the CH-4051 groups.

Secondary Efficacy Endpoints:

Patients in CH-4051treatment groups generally also showed improvements in hACR scores, ACR50 scores, ACR70 scores and DAS28 scores, with greater responses seen with increasing length of treatment and at higher doses of study medication. The MTX treatment group consistently showed higher responses than those seen with CH-4051 and these differences were significantly greater than CH-4051 at the two lowest doses ($p<0.05$).

The percent ACR20 responders increased with time in all study treatment groups and generally did not differ among the treatment groups.

In the ACR core set, there was generally a trend to improvement in symptoms with increasing length of treatment in all groups. A notable exception was the CRP measurement which improved with MTX treatment, but did not show a trend towards improvement in the CH-4051 groups. Improvement in the MTX group was greater than that in the CH-4051 groups in the patient assessment of pain and the physician global assessment of RA disease.

Safety results:

Overall there were 106/249 patients (42.6%) who experienced AEs in all dose groups. In the MTX group, 27/51 patients (52.9%) experienced AEs; in the CH-4051 0.3 mg/day group 19/50 patients (38.0%) experienced AEs; in the CH-4051 1.0 mg/day group 21/49 patients (42.9%) experienced AEs; in the CH-4051 3.0 mg/day group 15/50 (30%) experienced AEs; and in the CH-4051 3.0 mg/day + FA group, 24/49 patients (49.0%) experienced AEs. Overall, there were 10 patients withdrawn from the study due to an AE which included 4 patients from the CH-4051 0.3 mg/day group, 2 patients from the CH-4051 1.0 mg/day group, 1 patient from the CH-4051 3.0 mg/day group and 3 patients from CH-4051 3.0 mg/day + FA group.

Overall, 50/106 patients (47.2%) reported a mild AE as their highest severity AE, while 42/106 patients (39.6%) reported AEs that were of moderate intensity. Severe AEs (14/106, 13.2%) included acute cholecystitis and cholelithiasis, pneumonia, exacerbation of RA (7 AEs), muscle contracture, pain in extremity, chest discomfort, spinal operation and pregnancy. Chest discomfort and pneumonia were considered possibly related by the Investigator, pain in extremity was considered unlikely related.

The most common AEs were related to infections (17%), which were mostly urinary tract infections (6%), bronchitis (3%) and upper respiratory infections (2%).

The majority of AEs were considered not related or unlikely to be related to the study drug. There were 2 AEs in the MTX group (nausea and abdominal distension) and 3 AE each from CH-4051 0.3 mg/day group (all RA) and CH-4051 3.0 mg/day group (abdominal pain, headache and dizziness, hypertension) judged to be definitely related to the study drug.

Ten SAEs were reported by 7 patients during the course of the study. These included, Patient 11802 (acute cholecystitis and cholelithiasis) and Patient 11502 (discectomy and spinal fusion) from MTX group; Patient 11101 (benign pelvic neoplasm and vaginal absess), Patient 41007 (fractured left femur), and Patient 70301 (bilateral pneumonia) from the CH-4051 0.3 mg/day group; Patient 60405 (bleeding hemorrhoids) from the CH-4051 1.0 mg/day group; Patient 40304 (gastric ulcer and anemia) from the CH-4051 3.0 mg/day group. No SAEs were reported from CH-4051 3.0 mg/day + FA group.

There were no deaths during the study.

There were no clinically significant hematology parameters (hematocrit, WBC count, hemoglobin, RBC count, and platelet count) and clinical chemistry parameters (blood urea nitrogen, albumin, serum creatinine, total bilirubin, uric acid, and glucose) reported during the study in all the treatment groups.

Liver function tests (LFTs) were not impacted by study treatment. Overall ALT and AST levels greater than 1.5 times the upper limit of normal were observed with similar frequencies between groups. There did not seem to be a trend towards elevated LFTs with time in any of the treatment groups.

SUMMARY—CONCLUSIONS:

- CH-4051 demonstrated evidence of efficacy in the primary end-points of change in hACR score from Baseline to Week 12 and in percent of ACR20 responders at Week 12.
- There was evidence of a dose response in the change in hACR score in the CH-4051 dose groups.
- The MTX group had equal or greater responses in all measurement compared with CH-4051 groups.
- The majority of AEs were mild or moderate in all CH-4051 groups during the course of the study. CH-4051 was found to be safe and well tolerated at all dose levels.
- Given the excellent safety profile of CH-4051, it is likely that the anti-RA activity of higher doses of CH-4051 could be explored. It is possible that higher doses of CH-4051 would demonstrate greater efficacy than MTX and maintain an excellent safety profile.

Date of report: CSR 22 August 2013