2. SYNOPSIS

Title of Study:

A Phase IIB, Randomized, Multi-center, Double-blind, Placebo-controlled Trial of HMPL-004 in Patients with Mild to Moderate Active Ulcerative Colitis with or without Mesalamine

Investigators:

Multicenter; 40 investigators

Study Centers:

Multicenter; 40 centers in the United States, Canada, Romania, and Ukraine

Publication(s): None

Studied Period: 07 Feb 2008 to 13 Oct 2009	**Clinical Phase:** IIB

Objectives:

The primary objective of this study was to evaluate the efficacy of HMPL-004 given at 1200 mg/day or 1800 mg/day in 3 divided doses, compared with placebo, in subjects with mild to moderate ulcerative colitis as defined by the percent of subjects in each treatment group attaining clinical response at week 8, which is a decrease in the Mayo score from the baseline by ≥ 3 points AND ≥ 30% decrease in the Mayo score along with either a decrease in the rectal bleeding score ≥ 1 OR an absolute rectal bleeding score ≤ 1.

Secondary objectives were:

- To determine if there was a significant difference in the proportion of subjects in each treatment group with a clinical remission at week 8 as defined by a Mayo score ≤ 2 with no individual score > 1 in subjects treated with either dose of HMPL-004 as compared with placebo
- To determine if there was a significant difference in the proportion of subjects in each treatment group with a significant decrease from Baseline in the Mayo endoscopy sub-score AND absolute score ≤ 1 (mucosal healing)
- To determine the time to response as measured by the first assessment at which there was a significant difference between the proportion of subjects in either treatment group and placebo who showed a decrease in the partial Mayo score of ≥ 2 as compared to Baseline at week 2, 4, and 6
- To determine the time to response as measured by the first assessment when the mean partial Mayo clinical score in 1 of the treatment groups significantly decreased in relationship to the placebo group
- To compare the decrease in the mean and median Mayo score at baseline and week 8 in each treatment group
- To determine if there was a significant difference in any of the above efficacy measurements in subjects with/without mesalamine used as a concomitant medication
- To compare both dose levels of HMPL-004 with placebo using all of the measurements defined above
- To assess safety in subjects treated with HMPL-004 using the AE/SAE reporting, and other standard laboratory findings including hematology and blood chemistry, urinalysis and symptoms

An exploratory objective was to determine, in each treatment group, the proportion of subjects entering the study with elevated CRP values whose levels had normalized at the end of treatment.

Methodology:

This was a randomized, double-blind, placebo-controlled, multicenter study. Administration of mesalamine prior to and during the study was permitted but not required for inclusion, providing that the dose was stable; randomization was stratified by existing mesalamine use or non-use. Subjects were observed for an 8-week treatment period and a subsequent 4-week follow-up period.
This study was conducted in conformance with Good Clinical Practices (GCP).

Number of Subjects:

Planned: approximately 210 subjects (70 subjects per treatment group)
Analyzed: Intent-to-treat (ITT) = 223 (74 HMPL-004 1200 mg; 74 HMPL-004 1800 mg; 75 placebo)
Per-protocol (PP) = 207 (67 HMPL-004 1200 mg; 66 HMPL-004 1800 mg; 74 placebo)
Safety = 224 (75 HMPL-004 1200 mg; 74 HMPL-004 1800 mg; 75 placebo)

Diagnosis and Main Criteria for Inclusion:

Subjects had to meet the following inclusion criteria to be eligible for the study:

- Active confirmed mild to moderate ulcerative colitis defined by a Mayo score of 4 to 10, and with activity confirmed by study colonoscopy or sigmoidoscopy within 2 weeks prior to study entry
- Minimum Mayo endoscopy score of ≥1 at the time of study colonoscopy or sigmoidoscopy
- Age ≥ 18 years
- Adequate renal, hepatic, and bone marrow function
- Could be on mesalamine (or equivalent medications sulfasalazine, balsalazide, or olsalazine) if they had been on it for a least 4 weeks prior to randomization and the dose had been stable for ≥ 2 weeks prior to randomization

Test Product, Dose, Mode of Administration, Batch No:

HMPL-004 was supplied by the sponsor as 200 mg capsules. HMPL-004 was taken orally at a total daily dose of 1200 mg (400 mg [2 x 200 mg] 3 times daily), or 1800 mg (600 mg [3 x 200 mg] 3 times daily).

Batch numbers used in the study: 1283, 1307; Exp. 10OCT2009

Reference Product, Dose, Mode of Administration, Batch No:

Placebo was supplied by the sponsor as matched capsules (identical to HMPL-004 capsules without active drug), batch No. 1284; Exp. 10OCT2009

Duration of Treatment:

Treatment duration was 56 days (8 weeks) with a 28-day (4-week) follow-up.

Criteria for Evaluation:

Primary Efficacy Endpoint

The percentage of subjects with clinical response at week 8, defined as a decrease in Mayo score from Baseline ≥3 AND a 30% decrease in Mayo score, along with either a decrease in rectal bleeding score ≥1 OR absolute rectal bleeding score ≤1

Secondary Efficacy Endpoints based on Mayo Scoring

- Clinical remission
- Mucosal healing (endoscopy response)
- Time of first assessment when there was a significant difference between the proportion of subjects in either HMPL-004 group and placebo in partial Mayo response
- Time of first assessment when the mean change from baseline of partial Mayo score in either HMPL-004 group significantly decreased in relationship to the placebo group
- Time to partial Mayo response (decrease from baseline ≥2 in partial Mayo score)
- Change from baseline in partial Mayo score at 2, 4, 6, and 8 weeks
- Change from baseline full Mayo score at Week 8

Safety

Adverse events (AEs), clinical laboratory tests (hematology, blood chemistry and urinalysis), vital signs and body weight, 12-lead electrocardiogram (ECG), and physical examination findings. Only treatment-emergent AEs were considered.

Statistical Methods:

Primary efficacy analysis

Logistic regression of treatment categories (low dose, high dose, placebo) on clinical response at week 8, including significant covariates and 2-factor interaction terms: continuous covariates (age and baseline Mayo score) and categorical covariates (gender, race and mesalamine use). Regional classification adjusted for.

Secondary efficacy analysis

Further analysis of the clinical response included dose-response logistic regression. Primary endpoint was also expressed as unadjusted proportions by treatment, with corresponding chi-squared tests, overall and stratified by mesalamine use.

All above analyses for clinical remission and mucosal healing. ANCOVA for change in Mayo score from

baseline to week 8. Descriptive statistics shown for the endoscopy sub-score, including change from baseline.

Partial Mayo score at 2, 4, 6 and 8 weeks expressed as 95% t-distribution-based confidence intervals. Time to first partial Mayo response (a decrease of 2 or more points from baseline) analyzed with cumulative incidence plots (Kaplan-Meier) by treatment and corresponding plots over time of cumulative incidence ratios (CIRs) for comparison of HMPL-004 over placebo. Time to first partial Mayo response was also analyzed with stratified Cox regression of treatment, adjusted for significant covariates and regional classification.

Additional analyses required by FDA will be presented at a later date as an addendum to the present report.

Safety evaluation

Continuous variables summarized using descriptive statistics. Categorical variables summarized using frequency counts and percentages.

SUMMARY – CONCLUSIONS:

RESULTS:

Efficacy:

Efficacy outcomes broadly demonstrated statistical superiority to placebo of the higher HMPL-dose (1800 mg/day) but not the lower dose (1200 mg/day). Nevertheless, the lower dose generally produced positive results, that is, a greater degree of improvement than placebo, although less than that observed with the higher dose. For most endpoints so tested, dose-response models showed linearity in response, which can be considered confirmatory of activity.

Differing results were observed in the mesalamine and non-mesalamine strata. Subjects entering the study were not randomly assigned to receive concomitant mesalamine (or not), but simply continued their established mesalamine treatment (or did not initiate mesalamine treatment) during the study.

Primary endpoint: Overall, logistic regression demonstrated that HMPL-treated subjects had a higher rate of week 8 clinical response (P=0.0022). The 1800 mg per day HMPL-004 dose produced a clinical response rate of 72.6% that was statistically superior to placebo of 43.5% (odds ratio of 3.04, P<0.0001); the model showed significant interactions between treatment and mesalamine use, and between treatment and race. Additionally there was a significant linear dose response (P<0.0001).

The unadjusted analysis, stratified for mesalamine use, indicated a statistically significant difference in the higher HMPL-004 dose group compared to placebo in clinical response rate only among subjects treated with mesalamine (72.7% vs. 37.5%, P=0.0007 with mesalamine; 72.2% vs. 57.1%, P=0.3278 without mesalamine).

Secondary endpoints: Generally, secondary endpoints were consistent with the primary endpoint in relation to superiority to placebo of the higher HMPL-004 dose. Evidence of such superiority was observed primarily in subjects treated with mesalamine. Differences with P<0.05 in the logistic regression and unadjusted analyses comparing HMPL-004 doses with placebo in key secondary endpoints are summarized below:

Endpoint	Response Rate at Week 8			HMPL-004 Dose vs. Placebo with P<0.05	
	1200 mg/day	1800 mg/day	Placebo	Logistic Regression	Unadjusted (Chi-Squared)
Clinical response	55.0%	72.6%	43.5%	1800 mg P < 0.0001 Dose response P <0.0001	1800 mg P = 0.0008
Clinical remission	41.7%	45.2%	27.5%	1200 mg P = 0.0342 1800 mg P = 0.0450	1800 mg P = 0.0357
Mucosal healing	46.7%	59.7%	36.2%	1800 mg P = 0.0103 Dose response P = 0.0117	1800 mg P = 0.0073

Safety: The safety profile in subjects treated with HMPL-004 was generally similar to that in subjects receiving placebo. The incidence rate of AEs was 60.0%, 52.7%, and 60.0% in subjects treated with HMPL-004 1200 mg/day, 1800 mg/day, and placebo, respectively. The single most frequent AE was headache, reported in 10.7%, 5.4%, and 6.7% of subjects in the 1200 mg/day, 1800 mg/day, and

placebo groups, respectively.

No deaths occurred during the study. The reported SAEs were more or less equally distributed across treatment groups and were mainly attributable to the subjects' underlying disease. In the 1200 mg/day group, 2 subjects (2.7%) reported 3 SAEs (abdominal pain, diarrhea, and rectal hemorrhage); in the 1800 mg/day group, 2 subjects (2.7%) reported 5 events (ulcerative colitis, rectal hemorrhage, decreased hematocrit and hemoglobin, and dehydration); and in the placebo group, 2 subjects (2.7%) reported 4 events (ulcerative colitis and pilonidal cyst [1 subject], and ulcerative colitis and grand mal convulsion (1 subject]).

Treatment discontinuation due to AEs occurred in 9.3%, 8.1%, and 4.0% of subjects in the 1200 mg/day, 1800 mg/day, and placebo groups, respectively.

CONCLUSIONS:

HMPL-004 produced a superior response to placebo when administered to subjects with mild to moderate UC, based on Mayo score-derived clinical response and supported by all secondary efficacy outcomes. A dose response was observed; HMPL-004 at 1800 mg/day achieved a superior response to placebo, whereas the 1200 mg/day produced a response that, while greater than placebo, was not statistically significant. Stratification by mesalamine use demonstrated a higher response than placebo only among subjects receiving mesalamine who were in the 1800 mg/day HMPL-004 dose group.

HMPL-004 administered at doses of 1200 mg/day and 1800 mg/day, whether or not co-administered with mesalamine, was well tolerated and displayed a benign safety profile.

Date of the Report: 10 DEC 2010