2 SYNOPSIS

<table>
<tr><td>NAME OF COMPANY:
Holy Stone Healthcare Co., Ltd.</td><td colspan="2">INDIVIDUAL STUDY SYNOPSIS</td></tr>
<tr><td>NAME OF FINISHED PRODUCT:
Mesalamine and Sodium Hyaluronate

NAME OF ACTIVE INGREDIENT(S):
Mesalamine and Sodium Hyaluronate</td><td>INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER
Volume:

Page:</td><td>(FOR NATIONAL AUTHORITY USE ONLY)</td></tr>
<tr><td colspan="3">Title of Study: A Phase 2a, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled Trial of IBD98-M Delayed-release Capsules to Induce Remission in Patients with Active, Mild to Moderate Ulcerative Colitis</td></tr>
<tr><td colspan="3">Investigators: The list of Investigators is provided in Appendix 16.1.4 of the full clinical study report (CSR).</td></tr>
<tr><td colspan="3">Study Sites: A total of 9 investigative sites in Italy which received IEC/IRB approval to participate in this study enrolled at least 1 patient.</td></tr>
<tr><td colspan="3">Publication (Reference): None.</td></tr>
<tr><td colspan="2">Studied Period: 28 January 2016 to 02 July 2018</td><td>Phase of Development: IIa</td></tr>
<tr><td colspan="3">Objectives:
The primary objective was to compare the percentage of patients in ulcerative colitis remission at Week 6 for each of the 2 IBD98-M dose groups versus placebo (remission was defined as having a modified Ulcerative Colitis Disease Activity Index [UCDAI] score of ≤ 1, with a score of 0 for rectal bleeding and stool frequency, no mucosal friability, and a sigmoidoscopy score not exceeding 1).
The secondary objectives were as follows:
• To compare clinical improvement rates at Week 6 among treatment groups (defined as a ≥ 3 point reduction from Baseline in the modified UCDAI score)
• To compare endoscopic improvement at Week 6 among treatment groups (defined as a ≥ 1 point decrease in modified UCDAI mucosal appearance subscore)
• To determine the change in symptoms (rectal bleeding and stool frequency) from Baseline to each study visit among treatment groups
• To evaluate the safety and tolerability profile of IBD98-M
The exploratory objectives were as follows:
• To examine the effect of IBD98-M treatment on fecal calprotectin
• To examine any correlation between therapeutic response to IBD98-M and Baseline characteristics</td></tr>
<tr><td colspan="3">Methodology: It was a Phase 2a, multicenter, randomized, double-blind, parallel group, placebo-controlled trial in patients with active, mild to moderate UC, conducted as an exploratory proof-of-concept study to investigate the clinical efficacy of IBD98-M delayed-release capsules (in a fixed combination) over a 6-week treatment period and a 2-week follow-up period.</td></tr>
<tr><td colspan="3">Number of Patients: It was planned to enroll a total of 51 patients. A total of the 87 patients were screened, 51 patients were randomized, 17 patients in the IBD98-M 0.8 g/day group, 16 patients in the IBD98-M 1.2 g/day group, and 18 patients on the placebo group. Overall, 37 patients (72.5%) completed the study.</td></tr>
<tr><td colspan="3">Diagnosis and Main Criteria for Inclusion: The patients having a score of ≥ 4 and ≤ 10 on the</td></tr>
</table>

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modified UCDAI and a score of ≥ 1 on the endoscopy mucosal appearance subscore were enrolled in the study

Test Product: IBD98-M 200 mg

Dose: 0.8 g/day or 1.2 g/day

Mode of Administration: Oral

Batch Numbers: 24501001-01D002, 24501001-02D004, 24501001-02D007, 24501001-03B001, 24501001-05B001, 24501001-06B001, 24501001-01D003, 24501001-02D006, 24501001-03B002, 24501001-05B002, and 24501001-06B002

Duration of Treatment: Each patient received 3 capsules twice a day for a period of 6 weeks.

Reference Therapy: Placebo

Dose: Not applicable.

Mode of Administration: Oral

Batch Numbers: 24501001-01D001, 24501001-02D005, 24501001-03B003, 24501001-05B003, and 24501001-06B003

Criteria for Evaluation:

Efficacy: The primary variable was the percentage of patients in remission at Week 6.

Safety: The incidence and severity of all treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) throughout the study and systemic tolerance were assessed.

Study Endpoints:

Primary: The primary endpoint was the percentage of patients in remission at Week 6. Remission was defined as having a modified UCDAI score of ≤ 1, with a score of 0 for rectal bleeding and stool frequency, no mucosal friability, and a sigmoidoscopy score not exceeding 1.

Secondary:

- Proportion of patients with clinical improvement at Week 6 (defined as a ≥ 3 point reduction from Baseline in the modified UCDAI score)
- Proportion of patients with endoscopic improvement at Week 6 (defined as a ≥ 1 point decrease in modified UCDAI mucosal appearance subscore)
- Change in symptoms (rectal bleeding and stool frequency) from Baseline to each study visit
- Incidence and severity of all TEAEs
- Incidence and severity of SAEs
- Systemic tolerance (physical examination, vital signs, electrocardiograms [ECGs], and laboratory assessments of safety parameters)

Exploratory: The exploratory endpoint was the analysis of the reduction in fecal calprotectin.

Statistical Methods: Analyses were done on the intent-to-treat (ITT) population and the per-protocol population. The primary outcome, the percentage of patients in remission at Week 6, was calculated for each treatment group. An analysis of variance approach was used.

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SUMMARY OF RESULTS

Efficacy Results:

- The primary efficacy endpoint for the study was the percentage of patients in remission at Week 6. No statistically significant difference was observed between the placebo group and the IBD98-M 0.8 g/day ($p > 0.999$) group or the IBD98-M 1.2 g/day ($p > 0.999$) group for ITT population. Results for Per Protocol (PP) population and for sensitivity analysis were similar to the ITT population.
- No statistically significant difference was observed between the placebo group and the IBD98-M 0.8 g/day group or the IBD98-M 1.2 g/day group for clinical improvement at Week 6 for ITT population or for PP population.
- Higher reduction from Baseline was observed in the UCDAI score for the IBD98-M 1.2 g/day group (4.20) compared with the placebo group (1.80), and the IBD98-M 0.8 g/day group (1.17), at Visit 6, in the patients categorized as improved.
- No statistically significant difference was observed between the IBD98-M 0.8 g/day group or the IBD98-M 1.2 g/day group and the placebo group for endoscopic improvement at Week 6 for ITT population and PP population although higher reduction in endoscopic score was seen in IBD98-M 0.8 g/day group.
- No statistically significant difference was observed between the IBD98-M 0.8 g/day group ($p = 0.837$) or the IBD98-M 1.2 g/day group ($p = 0.335$) compared to the placebo group for mean change from Baseline to Visit 6 in UCDAI score. However, there was a change in the median score from Baseline to Visit 6 in UCDAI score which was larger in the IBD98-M 1.2 g/day versus IBD98-M 0.8 g/day versus placebo, although no statistical significance was seen.
- No statistically significant difference was observed between the IBD98-M 0.8 g/day group ($p = 0.133$) or the IBD98-M 1.2 g/day group ($p = 0.832$) compared to the placebo group for mean change from Baseline to Visit 6 in endoscopic score.
- No statistically significant difference was observed between the IBD98-M 0.8 g/day group or the IBD98-M 1.2 g/day group compared to the placebo group for rectal bleeding, stool frequency, and fecal calprotectin. However, no patients in the IBD98-M 1.2 g/day group had severe rectal bleeding and who shifted from mild to moderate or to severe rectal bleeding compared to the other groups.
- For UCDAI scores without including endoscopic score, higher reduction was observed in the IBD98-M 1.2 g/day group (-1.85) compared to the placebo group (-1.25), and the IBD98-M 0.8 g/day group (-0.36), in the patients categorized as improved.
- Changes in UCDAI scores without including endoscopic score and physician global assessment including withdrawn patients with completed UCDAI, higher reduction was observed in the IBD98-M 1.2 g/day group (-1.21) compared to the placebo group (-0.14) and the IBD98-M 0.8 g/day group (-0.15).
- Difference between the placebo group and the IBD98-M 0.8 g/day group or the IBD98-M 1.2 g/day group was not statistically significant for the Inflammatory Bowel Disease Questionnaire shift from Baseline to Visit 6 and for mental health summary score and

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reported health transition score components of SF 36. For physical health summary score component of SF-36, statistically significant difference was observed between the IBD98-M 0.8 g/day group (p = 0.010) and the placebo group and between the IBD98-M 1.2 g/day group (p = 0.032) and the placebo group, from Baseline to Visit 6.

Safety Results:

- Ten patients (58.8%) in the IBD98-M 0.8 g/day group, 11 patients (68.8%) in IBD98-M 1.2 g/day, and 15 (83.3%) patients in the placebo group reported at least 1 AE during the study.
- Overall, 33 patients (64.7%) reported at least 1 TEAE. The proportion of patients with at least 1 TEAE was higher in placebo group (72.2%) compared to IBD98-M 1.2 g/day (62.5%) and IBD98-M 0.8 g/day (58.8%) group.
- TEAEs of nausea and headache were reported as related TEAE for 2 patients (3.9%). TEAEs of dyspepsia, diarrhea, pyrexia, and dizziness were reported as related TEAE for 1 (2.0%) patient, each.
- No TEAE with severe intensity was reported during the study.
- No death was reported during the study.
- Only 1 SAE was reported in a screen failure subject.
- No SAE was reported during the study.
- No serious TEAEs were reported during the study.
- Overall, 6 patients (11.8%) were reported with at least 1 TEAE leading to study drug discontinuation. Of these, study drug discontinuation was reported for 4 (23.5%) patients in IBD98-M 0.8 g/day group and 2 patients (11.1%) in the placebo group.
- All clinically significant laboratory abnormalities were reported as TEAEs.
- None of the patients reported with abnormal clinical significant finding for vital signs, ECG, or physical examinations.
- None of the patient was reported to be positive for the pregnancy test.

Conclusions:

- In this proof-of-concept study, treatment with IBD98-M delayed-release capsules (0.8 mg/day and 1.2 mg/day) did not meet the primary endpoint as measured by percentage of patients in remission.
- Mean change from Baseline to Visit 6 in UCDAI score was higher in the IBD98-M 1.2 g/day group compared with the IBD98-M 0.8 g/day group and the placebo group. For physical health summary score component of SF-36, statistically significant difference was observed between the placebo group and the IBD98-M 0.8 g/day group (p = 0.010) and between the placebo group and the IBD98-M 1.2 g/day group (p = 0.032).
- The patients disease severity distribution in IBD98-M 1.2 g/day and 0.8 g/day included UCDAI score of 9 to 10 which was not the case for placebo, improvements in UCDAI score reduction and endoscopic improvement was seen, respectively, compared to placebo. Despite this distribution, IBD98-M 1.2 g/day group showed improvements in UCDAI score reduction; and IBD98-M 0.8 g/day showed endoscopic improvement, compared to

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the placebo group.

- No statistical significance was demonstrated in this study due to the limited number of patients per study arm.
- IBD98-M delayed-release capsules (0.8 mg/day and 1.2 mg/day) were found to be safe and well tolerated in this patient population. No new safety signals or unexpected safety findings were observed during the study.

Date of Report: 20 May 2019