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### 2.0 SYNOPSIS

<table>
<thead>
<tr>
<th>Title of Study:</th>
<th>Phase I, Multiple-dose Study of MLN0002 in Patients with Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Sponsor:</td>
<td>Takeda Pharmaceutical Company Limited</td>
</tr>
<tr>
<td>Name of Active Ingredient:</td>
<td>Humanized IgG1 monoclonal antibody to the human α_4β_7 integrin (Vedolizumab [INN])</td>
</tr>
<tr>
<td>Name of Finished Product:</td>
<td>MLN0002</td>
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<tr>
<td>Publication (reference):</td>
<td>None</td>
</tr>
<tr>
<td>Study Period (years):</td>
<td>23 June 2010 to 24 April 2012</td>
</tr>
<tr>
<td>Phase of Development:</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Number of Subjects:</td>
<td>Planned: 9-12 subjects: 3-6 subjects in Step 1 and 6 subjects in Step 2. Analyzed: 9 subjects: 3 subjects in Step 1 and 6 subjects in Step 2 for pharmacokinetics, pharmacodynamics, efficacy and safety analyses.</td>
</tr>
</tbody>
</table>

### OBJECTIVES

**Primary:** To investigate the pharmacokinetics, safety and tolerability of MLN0002 in Japanese patients with ulcerative colitis after multiple intravenous infusions of MLN0002 in an unblinded manner.

**Secondary:** To investigate the pharmacodynamics and efficacy of MLN0002 in Japanese patients with ulcerative colitis after multiple intravenous infusions of MLN0002.

### METHODOLOGY

This was a phase 1, open-label, multiple-dose study consisting of 2 steps. In Step 1, 150 mg of MLN0002 was intravenously administered on Days 1, 15 and 43 to 3 subjects with ulcerative colitis. In Step 2, 300 mg of MLN0002 was administered in the same manner to other 6 subjects. During the treatment period and the follow-up period, the subjects visited the study centers on Days 1, 8, 15, 29, 43, 57, 71, 99, 127, 155, 183, 211 and 239; and were hospitalized on Days 1-2 or 1-3 (applicable only to the first 3 subjects in Step 1), 15-16, and 43-44. MLN0002 serum concentrations were measured on Days 1, 2, 3 (applicable only to the first 3 subjects in Step 1), 8, 15, 29, 43, 44, 57, 71, 99, 127, 155, 183, 211, and 239. The measurement also was performed before and at 2, 6, 12 hours after administration on Day 1 and before and at 2, 6 hours after administrations on Days 15 and 43. Simultaneously, α_4β_7 receptor saturation was determined to evaluate the pharmacodynamics of MLN0002. Additionally, partial Mayo score was examined before administration on Days 1, 15 and 43 and on Days 71, 155 and 239 to evaluate the efficacy of MLN0002. An occurrence of adverse events (AEs) was monitored throughout the study period.

### Diagnosis and Main Criteria for Inclusion:

1. Subjects who had confirmed diagnosis of ulcerative colitis in accordance with the Draft Revised Diagnostic Criteria for Ulcerative Colitis (1998) issued by Research Group for Intractable Inflammatory Bowel Disease Designated as Specified Disease by the Ministry of Health and Welfare of Japan.
2. Subjects aged 18 to 70 years, inclusive, when giving consent to the study participation.
3. Subjects who were able to understand and comply with protocol requirements
4. Subjects who or whose subjects’ legally acceptable representative were able to give informed consent prior to the participation
5. Female subjects of childbearing potential (premenopausal or nonsterilized) who were sexually active with a nonsterilized male partner or nonsterilized male subjects who were sexually active with a female partner of childbearing potential, who agreed to use adequate contraception (as written in the informed consent form) from Screening to 28 weeks (196 days) after the last dosing of study drug
6. Subjects who had negative test result for hepatitis B surface (HBs) antigen, hepatitis C virus (HCV) antibody and human immunodeficiency virus (HIV) antigen/antibody and serological reactions for syphilis at Screening
7. Subjects weighed at least 40 kg at Screening and prior to study drug administration

Duration of Treatment:
6 weeks (3 doses: Day 1, Day 15 and Day 43).

Reference Therapy, Dose and Mode of Administration, Batch Number:
Not applicable.

Criteria for Evaluation:
Pharmacokinetics: MLN0002 serum concentrations
Pharmacodynamics: α4β7 receptor saturation
Efficacy: Partial Mayo score
Safety: adverse events (AEs), vital signs, body weight, electrocardiogram (ECG) findings, clinical laboratory results, progressive multifocal leukoencephalopathy (PML) evaluation, human antihuman antibodies (HAHA) assessment and neutralizing antibody assessment

Statistical Methods:
Pharmacokinetic analyses:
Summary statistics of MLN0002 serum concentrations were calculated by dose at each sampling point specified in the protocol and the time course of MLN0002 serum concentrations was tabulated (n, mean, standard deviation). In addition, summary statistics of the pharmacokinetic parameters (excluding AUMC(0-tlqc) and AUMC(0-inf)) were calculated by dose.

Safety analyses:
A treatment-emergent AE (TEAE) was defined as an event that occurring after the start of study drug or an aggravation of an existing complication. The incidence of TEAEs was summarized in terms of system organ class (SOC) and preferred term (PT) by treatment group. The incidence of TEAE was also summarized by severity, onset time, and relationship to the study drug. In addition, TEAEs leading to discontinuation and serious TEAEs were summarized by treatment group. In the event of a serious TEAE occurred, the incidence of the event was calculated.

In the analyses of AEs, summary statistics for vital signs, body weight, ECG findings, clinical laboratory results, PML evaluation, HAHA and neutralizing antibody assessment at baseline, each time point, and changes in value from baseline were to be calculated by dose. The results of assessment based on enumerated data and normal range were to be summarized by dose for each variable using a shift table that showed normal/abnormal determination, qualitative laboratory values, etc. before and after study drug.
SUMMARY OF RESULTS

Subject Disposition:
A total of 12 subjects were screened in 3 study centers in Japan. Of these, 9 subjects were enrolled. The reasons for screen failure were occurrence of pretreatment events and ineligibility for study participants. All 9 subjects received study drug. One of 3 subjects in 150 mg group discontinued the study due to an AE after completion of study drug administrations. Two subjects in 150 mg group and 6 subjects in 300 mg group completed the study.

Pharmacokinetics Results:
Following intravenous infusions of MLN0002 on Days 1, 15 and 43, serum concentrations of MLN0002 increased with increasing dose. Based on the mean AUC(0-336) and Cmax on Day 1, there was a 1.83- and 1.88-fold increase for a 2-fold increase between 150 mg and 300 mg groups, respectively. Based on the mean AUC(0-336) and Cmax on Day 43, there was a 2.02- and 1.84-fold increase for a 2-fold increase between 150 mg and 300 mg groups, respectively. The AUC(0-336) and Cmax of MLN0002 increased with increasing dose on Days 1 and 43.
Following intravenous infusion of MLN0002 at 150 mg and 300 mg, the serum concentrations of MLN0002 gradually decreased with mean T1/2 of 249.0 and 226.8 hours on Day 1, respectively, and with mean T1/2 of 376.3 and 416.8 hours on Day 43, respectively.
Predose MLN0002 concentrations on Days 15 and 43 were higher than the predose concentration on Day 1. The mean R(AUC) of serum MLN0002 was 1.4367 in 150 mg group and 1.5785 in 300 mg group. The mean R(Cmax) of serum MLN0002 was 1.3167 in 150 mg group and 1.2872 in 300 mg group. These results indicated minimal accumulation after multiple doses.

Pharmacodynamics Results:
The high inhibition of %MAdCAM was observed just after the first dose of MLN0002 on Day 1 and lasted throughout the treatment period in 150 mg and 300 mg groups. Following the last dose on Day 43, the high inhibition lasted up to Day 99 in 150 mg group and up to Day 155 in 300 mg group. As a result of combining the data from 150 mg and 300 mg groups, the change in combined mean and median inhibition rates of %MAdCAM indicated that the near maximal inhibition was achieved after the first dose and lasted throughout the treatment period.
The mean AUEC(0-336) and of MLN0002 on %MAdCAM was 29691.3%·hr in 150 mg group and 24217.0%·hr in 300 mg group on Day 1 and 26807.7%·hr in 150 mg group and 28272.7%·hr in 300 mg group on Day 43. The mean Emax of MLN0002 on %MAdCAM was 99.120% in 150 mg group and 95.306% in 300 mg group on Day 1 and 95.525% in 150 mg group and 98.132% in 300 mg group on Day 43. The mean AUEC(0-336) and Emax were similar between 150 mg and 300 mg groups and between Days 1 and 43.

Efficacy Results:
Following the last dose of MLN0002 on Day 43, 2 patients who did not meet the definition for clinical remission on Day 1 experienced a clinical response on Day 71 as measured by the partial Mayo score.

Safety Results:
Overall, 35 AEs were reported in 9 subjects (100.0%). Of those, 15 AEs were reported in 3 subjects in 150 mg group and 20 AEs were reported in 6 subjects in 300 mg group. The intensity of all AEs was mild or moderate but was not severe. The number of moderate AEs was 5 and 2 in 150 mg and 300 mg groups, respectively. They were colitis ulcerative (ulcerative colitis) (1), abdominal pain lower (1), colitis ischaemic (1), colon dysplasia (1), and frequent bowel movements (1) in 150 mg group, and ulcerative colitis (1) and ileus (1) in 300 mg group.
AEs related to the study drug included abdominal discomfort, abdominal pain lower, colitis ischaemic, ulcerative colitis, colon dysplasia, frequent bowel movements, headache, and upper respiratory tract inflammation in 150 mg group; ileus, myalgia, and rash in 300 mg group.
All 5 moderate AEs were reported to be related to the study drug in 150 mg group. In 300 mg group, 1 of 2 moderate AEs (ileus) was reported to be related to the study drug.
No dose-limiting toxicities were reported in the study.
Almost all AEs occurred after 14 days of the treatment period in 150 mg and 300 mg groups. AEs that occurred within 14 days after the first dose of MLN0002 on Day 1 were abdominal discomfort in 150 mg group and headache and rash in 300 mg group. No death was reported in the study.

A total of 2 serious adverse events (SAEs) were reported in the study. The number of subjects reporting SAEs was 1 each in 150 mg and 300 mg groups. The SAEs were colon dysplasia in 150 mg group and ileus in 300 mg group, and were reported to be related to the study drug but considered as related to the underlying disease.

No infusion reactions or no injection site reaction were reported in the study. There were no AEs leading to discontinuation of the study drug administration. One subject in 150 mg group discontinued the study due to a SAE (colon dysplasia) after completion of study drug administrations. There were no subjects who discontinued the study in 300 mg group.

Some changes from baseline were observed in some laboratory variables including hematology, blood coagulation tests, serum chemistry, urinalysis, vital signs and ECG parameters. But all of those changes were not clinically significant.

The mean C-reactive protein (CRP) levels tended to slightly decrease during the study period. However, mild increases in individual CRP levels also were observed in some subjects. There were no subjects having CRP of higher than 2.5 mg/dL during the study period. The mean erythrocyte sedimentation rates also tended to slightly decrease during the study period. However, there were some subjects who had relatively higher erythrocyte sedimentation rates, which ranged from approximately 20 to 75 mm/hr during the study period.

There were no subjects who reported any subjective symptoms based on the PML Checklist during the study period. This result indicated that no subjects developed PML or experienced signs and symptoms consistent with PML.

There were no subjects who tested positive for JC virus. This result indicated that there were no subjects with JC virus detected in plasma.

All 3 subjects in 150 mg group tested negative for HAHA. One of 6 subjects in 300 mg group tested positive for HAHA on Days 183, 211 and 239; this subject tested positive for neutralizing antibody on Day 183.

As a result of a 2-year follow-up survey, a subject in 150 mg group was reported to undergo colectomy for colon dysplasia, which was reported as a SAE, within 6 months after the last dose of study drug.

CONCLUSIONS

MLN0002 was well tolerated up to 300 mg intravenously administered on Days 1, 15 and 43 in Japanese patients with ulcerative colitis. MLN0002 serum concentrations increased with increasing dose and MLN0002 saturated α4β7 receptors at both 150 mg and 300 mg.

Date of Report: 17 January 2014