Protocol Addendum I6T-MC-AMAN (5)

A Phase 3, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Induction Study of Mirikizumab in Conventional-Failed and Biologic-Failed Patients with Moderately to Severely Active Ulcerative Colitis: Maximized Extended Enrollment Addendum

NCT03518086

Approval Date: 19-Mar-2018

1. Protocol Addendum I6T-MC-AMAN(5) A Phase 3, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Induction Study of Mirikizumab in Conventional-Failed and Biologic-Failed Patients with Moderately to Severely Active Ulcerative Colitis: Maximized Extended Enrollment Addendum

Mirikizumab (LY3074828)

This addendum is to be performed in addition to all procedures required by protocol I6T-MC-AMAN or any subsequent amendments to that protocol.

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Protocol Addendum(5) Electronically Signed and Approved by Lilly on date provided below.

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3. Rationale for Addendum

Regulatory agencies of some countries require local patient data from a specific number of patients for registration in their countries. This addendum provides a mechanism to meet these country-level registration requirements in a single pivotal study.

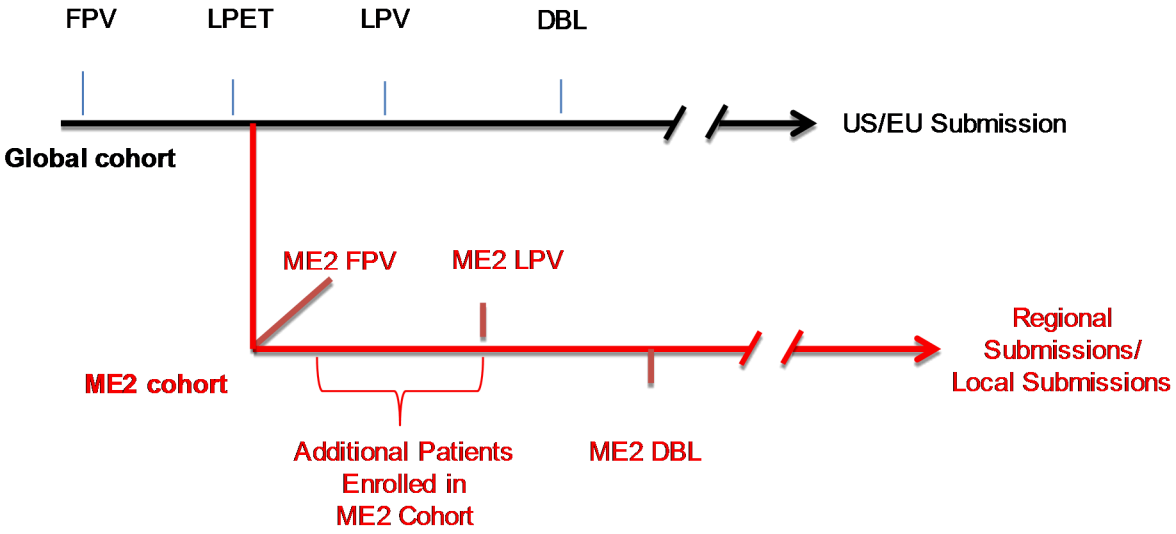
The purpose of this addendum is to enable patient enrollment to continue in these countries if the prespecified number of patients from the respective countries cannot be enrolled in the main protocol (Study I6T-MC-AMAN [AMAN]). Hereafter, patients enrolled in the main protocol will be referred to as the Global Cohort, and patients enrolled under the extended enrollment addendum will be referred to as the Maximized Extended Enrollment (ME2) Cohort. The number of patients enrolled in the ME2 Cohort will depend on the local guidelines and the number of patients from those countries already enrolled in the Global Cohort.

4. Protocol Additions

4.1. Extended Enrollment

Once the protocol milestone of last-patient-enters-treatment (LPET) for the Global Cohort is reached, enrollment will continue for those countries participating in the ME2 cohort, if needed, until sufficient numbers of patients are enrolled to meet the regulatory needs for those countries. Enrollment in the Global Cohort from the respective country is required before enrolling patients in the ME2 Cohort from the same country.

Figure AMAN(5).1 shows the milestones for enrollment in Study AMAN (Global Cohort and ME2 Cohort) through global and local submissions.



Abbreviations: DBL = database lock; EU = European Union; FPV = first patient visit; LPET = last patient entered treatment; LPV = last patient visit; ME2 = Maximized Extended Enrollment; US = United States.

Figure AMAN(5).1. Milestones for Global and ME2 Cohort enrollment through global and local submissions.

4.2. Investigational Plan

The objectives, enrollment criteria, randomization ratio, treatment, and evaluations of risk/benefit for patients enrolled in the ME2 Cohort will be identical to those for patients enrolled in the Global Cohort from these countries, including both those described in the main protocol, as well as in any applicable protocol addenda.

4.3. Discontinuation of Study in Extended Enrollment Phase

Enrollment in the ME2 Cohort will be discontinued if results from the Global Cohort demonstrate futility, lack of efficacy, and/or an unacceptable safety profile.

4.4. Statistical and Analytical Plans

4.4.1. Determination of Sample Size

The total number of patients enrolled in each country is based on the minimum number of patients needed to support local registration. The number of patients enrolled in the ME2 Cohort is dependent on the number of patients enrolled from each of the respective countries in Global Cohort as part of the protocol-defined sample size of 1160 patients. If a country fully meets patient enrollment needs in the Global Cohort, no patient will be enrolled under this addendum for that country.

4.4.2. Statistical and Analytical Plans

4.4.2.1. General Considerations

The benefit/risk profile to support global registrations will be based on the safety and efficacy analyses of Global Cohort. Patients enrolled in the ME2 Cohort will not be included in the primary global analysis, as described in the statistical methods outlined in the main protocol of Study AMAN.

Patients enrolled in the ME2 Cohort will be analyzed separately using the statistical methodology described in the main protocol of Study AMAN. The data from the ME2 Cohort will be used in the respective countries to demonstrate similarity between local patients and the intent to treat (ITT) population enrolled in the Global Cohort. Patients in the ME2 Cohort (and their investigators) will remain blinded until the ME2 Cohort is locked and unblinded.

As necessary, country-specific efficacy and safety analyses will be summarized for enrolled patients from each of the participating countries by pooling each country's patients from the Global Cohort and the ME2 Cohort. All analyses will be for descriptive purposes only. Details of the analyses are described in the statistical analysis plan.

4.4.2.2. Interim Analyses

No interim analyses are planned for the ME2 Cohort.

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