CLINICAL STUDY PROTOCOL

Protocol Number: BT-11-201; Phase 2

US IND Number: 138071

EudraCT Number: 2018-005086-39

A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate Efficacy and Safety of Oral BT-11 in Mild to Moderate Ulcerative Colitis

Protocol Amendment 03
03 November 2020

Sponsor: Landos Biopharma Inc.

Clinical Research Organization: [redacted]

PROTOCOL SYNOPSIS

Title

A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate Efficacy and Safety of Oral BT-11 in Mild to Moderate Ulcerative Colitis

Objectives

The primary objective of this study is to establish the efficacy of oral BT-11 in inducing clinical remission at Week 12 in subjects with mild to moderate ulcerative colitis (UC).

The secondary objectives of this study are to evaluate the following at Week 12:

1. The effects of BT-11 on disease activity measured by symptoms, endoscopy, histology, and biomarkers
2. Health-related quality of life
3. The pharmacokinetic (PK) parameters of BT-11
4. Safety

The exploratory objectives of this study are to evaluate the following through Week 30:

1. The effects of BT-11 on disease activity measured by symptoms, endoscopy, histology, and biomarkers
2. Health-related quality of life
3. The PK parameters of BT-11
4. Safety
5. Target engagement and mechanism of action
6. The association of drug exposure in colonic mucosal tissue biopsies with clinical, endoscopic, histopathologic, cellular, and molecular outcomes

Study Design

This is a phase 2 randomized, placebo-controlled, double-blind, parallel-group multicenter study with an optional open-label extension (OLE) period. The purpose of this study is to evaluate the efficacy and safety of oral BT-11 compared to placebo in subjects with mild to moderate UC.

This study includes 3 periods: induction, maintenance, and an optional OLE period.

Induction Period:

Following a 28-day screening period, a total of 195 subjects with mild to moderate UC (total Mayo Score 4-10; Mayo endoscopic subscore [MES] ≥ 2) are planned to be enrolled into this study from approximately 46 sites in Europe and the United States. Eligible subjects will be randomized in a 1:1:1 ratio to receive BT-11 low-dose (500 mg), BT-11 high-dose (1,000 mg) or placebo. Each of the treatment arms will comprise 65 subjects. The randomization will be stratified by prior exposure to biologic therapy for UC (yes/no; exposed population limited to 30% of total sample) and corticosteroid use at baseline (yes/no).

A data lock and final induction phase analysis of the Week 12 primary endpoint, Week 12 key ranked secondary endpoints, and Week 12 AE listings will be conducted after all subjects have reached Week 12. At the Week 12 Visit, subjects who are responders (clinical response and/or clinical remission) and meet all other maintenance continuation requirements may continue blinded study drug until central endoscopy results are available (within approximately 1 week of the endoscopy) for confirmation of eligibility for the maintenance period. Subjects who are nonresponders at Week 12, or who lose response during the maintenance period, or who complete the Week 30 study will be eligible for the optional OLE period.

Maintenance Period:

All subjects who complete the induction period and are responders at Week 12 will enter the 18-week maintenance period. Subjects who continue to the maintenance period will receive the same blinded study drug as the induction period until Week 30. If a subject loses response during the maintenance period, they may have the option to move into the OLE after completing the early termination visit.

OLE Period:

Subjects who a) completed the induction period and were nonresponders at Week 12, or b) lost response during the maintenance period, or c) completed the blinded maintenance period (through Week 30) of that study will have the option to enter the OLE period. Eligible subjects will start open label treatment within approximately 2 weeks after their last dose of study drug in the induction or maintenance period. Subjects who are classified as nonresponders after 12 weeks of therapy in the OLE will be discontinued from the study. Subjects who continue to respond to study treatment will have the option of remaining on BT-11 until the therapy becomes commercially available, or until the sponsor decides to terminate the study or offers an alternate OLE study.

Study Population

The study will include 195 subjects with mild to moderately active UC. Subjects with prior exposure to biologic therapy will be limited to 30% of the total sample. After 58 subjects with prior exposure to biologic therapy have been randomized into the induction period, recruitment will be limited to biologic-naïve subjects.

Key inclusion criteria: male and female subjects aged 18 to 75 years with a diagnosis of UC for at least 3 months; mild to moderate UC defined by a total Mayo Score of 4 to 10 with MES $\geq$ 2 (confirmed by central reader); prior biologic must have stopped at least 8 weeks before study and previous biologic treatment failure is limited to 1 class of biologic; 5-aminosalicylates (max 4.8 g/day) and oral corticosteroids (max 20 mg/day prednisone or equivalent) must be stable for the 12-week induction period.

Key exclusion criteria: severe UC defined by modified Truelove and Witts criteria; disease activity limited to distal 15 cm (proctitis); treatment with immunosuppressant within 25 days prior to randomization; current bacterial or parasitic pathogenic enteric infection; live virus vaccination within 1 month prior to screening.

Maintenance Continuation Criteria:

Key maintenance continuation criteria: meeting eligibility requirements for clinical response and/or clinical remission at Week 12, centrally read confirmation of response is received within 2 weeks of completing the Week 12 visit, and agreeing to a corticosteroid tapering regimen starting at Week 12 with maintenance of stable doses of any other nonprohibited concomitant medications for UC during the rest of the study.

OLE Continuation Criteria:

Key OLE inclusion criteria: All subjects who a) completed the induction period of that study and were nonresponders at Week 12 of the induction period, or b) lost response during the maintenance period, or c) completed the blinded maintenance period (through Week 30). Eligible subjects will start open label treatment within approximately 2 weeks after their last dose of study drug in the induction or maintenance period.

Key OLE exclusion criteria: Experiencing a serious adverse event (SAE) that was considered related to study drug during participation in the induction or maintenance period; pregnancy or lactation in females; diagnosis, medication, or change in circumstance since enrollment in the induction or maintenance period that meets certain exclusion criteria from that period.

Treatments, Dosage, and Administration

Subjects will be randomized to receive BT-11 low-dose (500 mg), BT-11 high-dose (1,000 mg), or placebo once daily for 12 weeks during the induction period of the study. Subjects who continue to the maintenance period will remain in the same blinded treatment group to which they were originally randomized. Authorized personnel at the investigative site will administer the first dose of the study drug or placebo in a blinded fashion. All tablets administered (placebo and BT-11) will have the same appearance and size. Each subject will receive blister packs of the study drug (high-dose BT-11, low-dose BT-11, or placebo).

In the OLE, all subjects will receive BT-11 high-dose (1,000 mg) and study treatment will not be blinded.

A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate Efficacy and Safety of Oral BT-11 in Mild to Moderate Ulcerative Colitis

BT-11-201, Phase 2

STATISTICAL ANALYSIS PLAN

Version 01
November 6, 2020

Status: Effective

Prepared by: [redacted]

Sponsor: Landos Biopharma Inc.

Efficacy Evaluations

Induction and Maintenance:

Primary Efficacy Endpoint:

- Clinical remission rate at Week 12, defined using the 3-component modified Mayo Score as a rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1, and an endoscopic subscore of 0 or 1

Statistical Methods

A sample size of 65 randomized subjects to each of 3 treatment groups during the induction period is expected to provide evaluable data on approximately 63 subjects per group at Week 12. This sample size will allow for the detection of a 17-percentage point change in remission rate (assuming a 5% placebo endoscopic remission rate) between groups, with a type I error rate of < 0.05 and 80% power.

Efficacy analyses will primarily be based on the modified intent-to-treat (mITT) analysis set. A robustness analysis of the primary and key secondary efficacy endpoints will also be performed on the per-protocol (PP) analysis set. Statistical tests will be 2-sided and performed at the 0.05 level of significance.

The proportion of subjects with clinical remission at Week 12 (defined using the 3-component modified Mayo Score as a rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1, and an endoscopic subscore of 0 or 1) for each group will be tested with a Cochran-Mantel-Haenszel test, stratified with respect to previous use of biologic therapy (yes/no; exposed population limited to 30% of total sample) and oral corticosteroid use at baseline (yes/no).

A closed hierarchical procedure will be used to control for multiple comparisons. The order of testing will begin with high dose versus placebo at Week 12. If this result is significant at the 2-sided $P < .05$ then the low-dose versus placebo at Week 12 will be tested, followed by subsequent ranked key secondary analyses. In this regard, the first ranked secondary endpoint will be tested first for the high dose, and subsequently for the low dose provided $P < .05$ for the high dose. Testing will continue in a similar manner for the subsequent ranked secondary endpoints with high dose tested prior to low dose. If at any point in this sequential procedure the $P < .05$ is not met, the testing procedure will be terminated. All subsequent analyses would be considered exploratory.

A data lock and final induction phase data analysis of Week 12 primary endpoint, Week 12 key ranked secondary endpoints, and Week 12 AE listings will be performed when all subjects have completed the induction period (or discontinued study treatment). To minimize any bias being introduced into the analysis, all data during the assessment period associated with the primary endpoint, key ranked secondary endpoints, or AE listings as of Week 12 must have been monitored, the induction period statistical analysis plan (SAP) must be finalized and approved, and definitions of analysis populations must be finalized (including classification of significant protocol deviations and decision regarding exclusion of any subjects from the induction study analysis) before the partial database lock and before unblinding.

As this will be the final analysis of the primary and key ranked secondary endpoints, no adjustment of type I error will be performed. The induction analysis will be conducted by a limited number of preidentified team members who do not have direct site contact or data entry/validation responsibilities. Unblinding details will be specified in the unblinding plan section of the SAP or in a separate unblinding plan document. Information that may unblind the study during the final analyses of induction data will not be reported to study sites or the blinded study team until the study has been unblinded.

A second analysis (maintenance data lock and analysis) will be performed to assess the remaining Week 12 secondary and exploratory endpoints and the Week 30 efficacy and safety results after all subjects have completed the maintenance period (or discontinued study treatment). No type 1 error adjustment will be necessary for the analyses of the additional non-ranked secondary endpoints and exploratory endpoints.

This will be the final analysis for many of the secondary and exploratory efficacy endpoints out to Week 30. Once the maintenance data lock is complete, the study will be unblinded.

Before each data lock, the applicable SAP must be finalized as well as coding of events, medications and assessment of any major protocol deviations.

The final database lock and analysis of the OLE period data will be carried out when the study ends.