CLINICAL STUDY PROTOCOL

Protocol Number: BT-11-202; Phase 2

US IND Number: 128490

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A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate Efficacy and Safety of Oral BT-11 in Moderate to Severe Crohn's Disease

Protocol Version 1.1
01 April 2021

Sponsor: Landos Biopharma Inc.

Clinical Research Organization: [redacted]

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PROTOCOL SYNOPSIS

Title

A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate Efficacy and Safety of Oral BT-11 in Moderate to Severe Crohn's Disease

Objectives and Endpoints

Primary Objective

The primary objective of this study is to assess the proof-of-concept efficacy and safety of oral BT-11 in inducing clinical remission and endoscopic response at Week 12 in subjects with moderately to severely active Crohn's disease (CD).

Study Design

This is a phase 2, randomized, placebo-controlled, double-blind, parallel-group, multicenter study. The purpose of this study is to evaluate the proof-of-concept efficacy and safety of oral BT-11 compared to placebo in subjects with moderately to severely active CD to estimate the effect size and efficiently power future phase 3 studies. Approximately 100 sites will participate from Europe and the United States.

A total of 150 subjects were planned to be randomized in a 1:1 ratio, in a centralized manner, to receive BT-11 880 mg or placebo. Each of the treatment arms will comprise 75 subjects. The randomization will be stratified by prior exposure to biologic therapy for CD (yes/no; exposed population limited to 50% of total sample) and corticosteroid use at baseline (yes/no).

The study will consist of a 28-day screening period, a 12-week induction period, an 18-week maintenance period, and a 2-week post-treatment safety follow-up period.

A final analysis of induction phase data (induction data lock and analysis), of the Week 12 primary endpoint, Week 12 key ranked secondary endpoints, and Week 12 adverse event (AE) listings, will be conducted after all subjects have reached Week 12. At Week 12, subjects who are clinical responders (defined by a Crohn's Disease Activity Index [CDAI] decrease from baseline $\geq$ 100 points or CDAI < 150) or endoscopic responders (defined by a 50% reduction from baseline in the Simple Endoscopic Score for Crohn's Disease [SES-CD] score), 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 additional 18-week maintenance period. If a subject is a potential endoscopic responder at Week 12 and requires centrally read confirmation of SES-CD score as a qualifying continuation criteria (i.e., doesn't qualify for maintenance based on clinical response or remission alone), then the SES-CD score must be confirmed by central reading. Subjects who are non-responders at Week 12, or who lose response during the maintenance period, or who complete the Week 30 study will be eligible for a separate open-label extension (OLE) study.

Study Population

The study will include 150 subjects with moderately to severely active CD. Subjects with prior exposure to biologic therapy will be limited to 50% of the total sample. After 75 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: subjects aged 18 to 75 years with a diagnosis of CD for at least 3 months; moderately to severely active CD as defined by: a CDAI score of 220-450, and an SES-CD scored $\geq$ 6 ($\geq$ 4 for isolated

ileitis) (centrally read); prior biologic must have stopped at least 8 weeks before randomization (or within 4 weeks prior to randomization, if no detectable drug levels by validated or commercial assay) and previous biologic treatment failure is limited to 1 class of biologic (if applicable); 5-aminosalicylates (max 4.8 g/day) and oral corticosteroids (max 20 mg/day prednisone or equivalent) must be stable for the duration of the 12-week induction period.

Key exclusion criteria: ulcerative colitis; imminent risk of ileocolectomy; symptomatic bowel stricture, ostomy or ileoanal pouch, stenoses, or short gut syndrome; recent (within 2 months) abscess, unless drained and treated at least 6 weeks before randomization; history of bowel resection or diversion within 3 months prior to screening; use of apheresis ≤ 2 weeks prior to screening; treatment with an immunosuppressant within 25 days prior to randomization; known current bacterial or parasitic pathogenic enteric infection; live virus vaccination within 12 weeks of screening.

Maintenance continuation criteria: meeting eligibility requirements for clinical response and/or clinical remission at Week 12 or endoscopic response at Week 12, centrally read confirmation of response is received within 1 week 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 CD during the rest of the study.

Treatments, Dosage, and Administration

Subjects will be randomized to receive BT-11 880 mg or placebo once-daily for 12 weeks during the induction period of the study. Subjects who continue on 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. This study is double-blinded. Alls administered (placebo and BT-11) will be identical in appearance and size. According to the randomization scheme, each subject will receive PE bottles of either the study drug or placebo.

Statistical Analysis Plan

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Statistical Methods

A total sample size of 150 subjects randomized in a 1:1 ratio to BT-11 880 mg or placebo (75 subjects per treatment group) is expected to provide evaluable data on approximately 74 subjects per group at Week 12 (1% attrition rate).

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 first coprimary efficacy endpoint is the proportion of subjects achieving clinical remission at Week 12 (defined by a CDAI score < 150). Inference will be determined with a Cochran-Mantel-Haenszel test and stratified with respect to previous use of biologic therapy and corticosteroid use at baseline. As this is a proof-of-concept study, success in this trial is not intimately linked to achieving statistical significance on primary and key secondary endpoints.

The issue of multiplicity of secondary measurements will be handled by statistical testing of these outcomes in a hierarchical fashion. The order of secondary endpoints is described above. If the primary outcome shows significance, tests will be conducted on secondary outcomes until a non-significant p-value is found ($P > 0.05$). Once a nonsignificant p-value occurs, all subsequent significance tests will be considered exploratory in nature.

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 performed when all subjects have completed the induction period (or discontinued study treatment). To minimize any bias being introduced into the analyses, all data associated with the primary and key secondary endpoints during the assessment period must have been monitored, the induction period SAP must be finalized and approved, and the 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 database lock and unblinding.

As this will be the final analysis of the primary endpoints and key ranked secondary endpoints, no adjustment of type I error will be performed. The induction analysis will be performed 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 statistical analysis plan or a separate unblinding plan document. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.