A Phase 3, Randomised, Double-Blind, Placebo-Controlled Study of Xenomalib in Adult Patients with Moderate-to-Severe Rheumatoid Arthritis

Sponsor: Helix Biotherapeutics, Inc.
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1. INTRODUCTION AND BACKGROUND

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterised by persistent joint inflammation, progressive joint damage, and significant impairment of physical function and quality of life. The global prevalence of RA is approximately 0.5·1% of the adult population.

Xenomalib (HBX-001) is an investigational monoclonal antibody that selectively inhibits the JAK1/TYK2 pathway. Preclinical studies have demonstrated potent anti-inflammatory activity with a favourable safety profile.

This Phase 3 study is designed to evaluate the efficacy and safety of Xenomalib versus placebo in adult patients with moderate-to-severe active RA who have had an inadequate response to at least one conventional synthetic DMARD.

2. STUDY OBJECTIVES

3. STUDY DESIGN

2.1 Primary Objective
To evaluate the efficacy of Xenomalib 200 mg SC every 4 weeks compared with placebo in reducing signs and symptoms of RA as measured by ACR20 response at Week 24.

2.2 Secondary Objectives
- ACR50 and ACR70 response rates at Week 24
- Change from baseline in DAS28-CRP at Week 24
- Clinical remission (DAS28-CRP < 2.6) at Week 24

3.1 Overview
This is a 52-week, multicentre, randomised, double-blind, placebo-controlled study. Patients will be randomised 2:1 to receive Xenomalib 200 mg SC or matching placebo every 4 weeks for 52 weeks.

4. STUDY POPULATION

4.1 INCLUSION CRITERIA

Patients must meet ALL of the following inclusion criteria to be eligible:

IC-01. Age · 18 years at the time of signing the informed consent form.

IC-02. Diagnosis of RA according to the 2010 ACR/EULAR classification criteria for at least 6 months prior to Screening.

IC-03. Moderate-to-severe active disease defined as:
(a) · 6 tender joints (of 68 assessed) AND
(b) · 6 swollen joints (of 66 assessed) AND
(c) hsCRP > 5 mg/L OR ESR > 28 mm/hour at Screening.

IC-04. Inadequate response to at least one conventional synthetic DMARD (e.g., methotrexate, leflunomide, sulfasalazine) administered for
· 12 weeks at an adequate therapeutic dose.

IC-05. Female patients of childbearing potential must agree to use highly effective contraception throughout the study and for 6 months after the last dose of study drug.

IC-06. Able to provide written informed consent and comply with all study procedures.

4.2 EXCLUSION CRITERIA

Patients meeting ANY of the following criteria are NOT eligible for this study:

EC-01. Age < 18 years.

EC-02. Prior exposure to any JAK inhibitor (e.g., tofacitinib, baricitinib, upadacitinib) or any biologic DMARD (e.g., TNF inhibitor, IL-6 inhibitor, abatacept, rituximab).

EC-03. Active, serious infection requiring IV antibiotics within 4 weeks prior to Baseline, or any chronic or recurrent infection considered by the Investigator to place the patient at unacceptable risk.

EC-04. History of or current active tuberculosis (TB). Patients with latent TB who have received adequate prophylactic treatment (· 4 weeks of isoniazid or equivalent) prior to Baseline may be enrolled.

EC-05. Known or suspected current malignancy, or history of malignancy within the past 5 years, with the exception of adequately treated non-melanoma skin cancer or cervical carcinoma in situ.

EC-06. Pregnancy or breastfeeding at Screening or Baseline. Women of childbearing potential with a positive serum pregnancy test at Screening.

4.2 EXCLUSION CRITERIA (continued)

EC-07. Severe renal impairment defined as eGFR < 30 mL/min/1.73 m² (CKD-EPI formula) at Screening.

EC-08. Severe hepatic impairment (Child-Pugh Class C) or ALT or AST > 3× ULN at Screening.

EC-09. Clinically significant cardiovascular disease within 12 months prior to Baseline, including myocardial infarction, unstable angina, stroke, or New York Heart Association (NYHA) Class III·IV heart failure.

EC-10. Known HIV infection, active hepatitis B (HBsAg positive), or active hepatitis C (HCV RNA positive) at Screening.

EC-11. Absolute neutrophil count (ANC) < 1,000 cells/·L, haemoglobin < 8.0 g/dL, or platelet count < 100,000 cells/·L at Screening.

EC-12. Current or recent (within 30 days prior to Baseline) use of any live attenuated vaccine, or planned vaccination during the study.

EC-13. Known hypersensitivity to any component of the study drug formulation.

EC-14. Participation in any other clinical study involving an investigational product within 30 days or 5 half-lives (whichever is longer) prior to Baseline.

5. STUDY PROCEDURES

5.1 Screening Period (Days ·28 to ·1)
Patients will attend a Screening Visit to assess eligibility. The following assessments will be performed: informed consent, medical history, physical examination, vital signs, 12-lead ECG, laboratory assessments (haematology, chemistry, urinalysis), serum pregnancy test (women of childbearing potential), TB test (QuantiFERON-TB Gold or equivalent), and prior/concomitant medication review.

5.2 Baseline Visit (Day 1)
All screening assessments will be repeated and eligibility confirmed prior to randomisation. Patients will receive the first dose of study drug on Day 1.

5.3 Treatment Period (Weeks 1·52)
Study drug will be administered every 4 weeks (±3 days). At each visit: joint counts, PGA, PhGA, hsCRP/ESR, and concomitant medication review. Safety laboratory assessments at Weeks 4, 12, 24, 36, and 52.

6. STATISTICAL ANALYSIS PLAN

6.1 Analysis Populations
The Intent-to-Treat (ITT) population includes all randomised patients who received at least one dose of study drug. The Per-Protocol (PP) population includes all ITT patients without major protocol deviations.

6.2 Primary Endpoint Analysis
The primary endpoint (ACR20 response at Week 24) will be analysed using a logistic regression model with treatment group as the fixed effect and baseline DAS28-CRP, prior biologic use (yes/no), and geographic region as covariates. Non-responder imputation (NRI) will be used for missing data.

6.3 Sample Size
Assuming 60% ACR20 response rate for Xenomalib and 25% for placebo, with 80% power and two-sided · = 0.05, a total of 240 patients (160 active: 80 placebo) are required.