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Design: Phase 2/3, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Prospective EBO-301 Study to Assess the Efficacy, Safety, and PK of Oral Epetraborole (EBO) Versus Placebo (PBO), Each in Combination with an Optimized Background Regimen (OBR), in Patients with Treatment-Refractory *Mycobacterium avium* Complex Lung Disease (TR-MAC-LD)

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INTRODUCTION

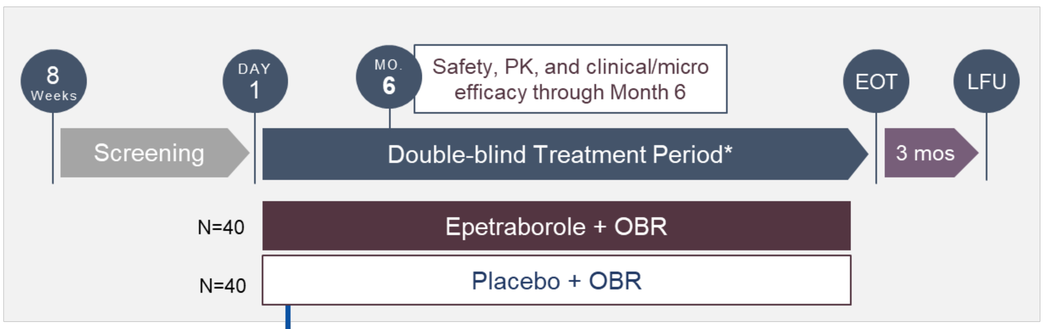
- AN2 is developing epetraborole (EBO) tablets for the treatment of serious infections for which there is a high unmet medical need for new antimicrobial therapy in combination regimens, such as lung disease (LD) caused by nontuberculous mycobacteria (NTM)
- *Mycobacterium avium* complex (MAC) currently accounts for approximately 80% of NTM-LD in the US and Europe and approximately 93% in Japan[1,2]
- Treatment options for TR-MAC-LD are limited and may be poorly tolerated[3,4]
- EBO is an oral antibiotic with a novel MOA and is an inhibitor of bacterial LeuRS, which is an essential enzyme in protein synthesis
- EBO has broad-spectrum activity against the most common causative pathogens of NTM-LD (including MAC), reaches therapeutic concentrations in alveolar macrophages, and is efficacious alone and in combination with standard of care antimycobacterial agents in acute and chronic mouse models of MAC-LD

METHODS

Study Design and Population

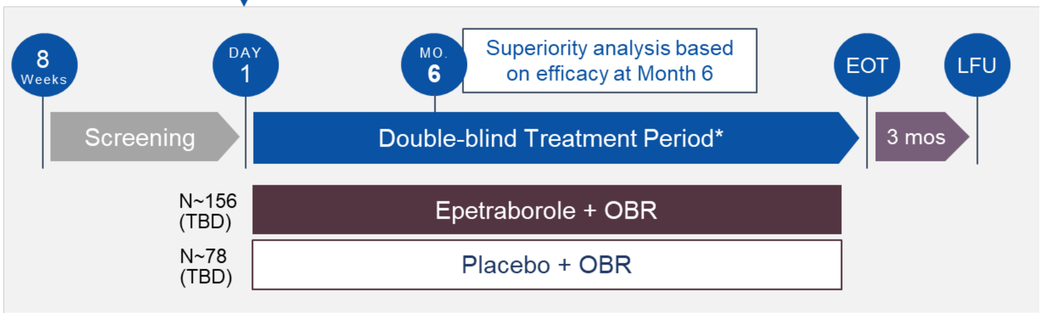
- Global, double-blind, operationally seamless Phase 2/3 study randomizing adults with TR-MAC-LD to either EBO or placebo (PBO) on top of an optimized background regimen (OBR)
- OBR agents were per standard of care, at the discretion of the Investigator, and not defined by the Sponsor or the protocol. There was no requirement for susceptibility of the baseline pathogen to any OBR component
- In Phase 2, ~80 patients were to be randomized in a 1:1 ratio (500 mg EBO tablets: matching PBO tablets) and stratified by baseline use of ALIS and age (<65 or ≥65). Patients of all MAC-LD clinical phenotypes (eg, fibrocavitary) and of any duration since initial diagnosis were eligible for enrollment
- Treatment duration was for a minimum of 6 months and up to 16 months, depending on outcome and timing of sputum culture results; patients failing to achieve sputum culture conversion (SCC) by Month 6 of treatment were discontinued from treatment
- Assessments included symptom-based clinical responses (including multiple patient-reported outcome [PRO] measures), microbiological responses, safety, and EBO PK
- The study incorporated a blinded psychometric analysis of the novel $MACrO_2$ PRO instrument designed to assess symptom response in TR-MAC-LD. The $MACrO_2$ PRO measure includes 7 symptoms and an additional item questioning the patient as to which "key" symptom they most wanted to see improved
- Endpoints included symptom-based clinical response (primary in the US), SCC (primary outside the US), and various secondary measures including SCC in the US
- The data from the Phase 2 study were to inform selection of the primary outcome measure in Phase 3 and final targeted sample size

Phase 2 Part



Seamless enrollment,
No pause between Phase 2 and 3

Phase 3 Part



* Patients who culture convert will be treated for 12 months from 1st negative culture per treatment guidelines.
EOT = End-of-Therapy; LFU = Late Follow-up; OBR = Optimized Background Regimen; TBD = Final sample size to be confirmed based on Phase 2 Part data

METHODS (*continued*)

Diagnostic criteria were rigorously selected to ensure that enrolled patients had TR-MAC-LD, and not MAC colonization.

Key Inclusion Criteria:

Patients with a diagnosis of TR-MAC-LD, i.e., a respiratory specimen positive for MAC despite receiving ≥2 antimycobacterial agents for ≥6 months, meeting all the following criteria:

a. *Microbiological criteria*:
   - sputum or deep bronchial specimen collected within 6 months prior to enrollment
   - ≥1 Screening MAC-positive sputum sample

b. *Clinical criteria*: ≥2 patient-reported ongoing clinical symptoms, the "key" symptom of which must be of moderate or greater severity:
   - Cough with sputum production
   - Cough without sputum (dry cough)
   - Chest congestion
   - Hemoptysis
   - Dyspnea (shortness of breath)
   - Fatigue
   - Night sweats or unusual sweating

c. *Radiographic criteria*: Non-contrast chest CT scan within 6 months prior consistent with MAC-LD

d. *OBR criteria:* patient-specific combination regimen of ≥2 antimycobacterial agents, administered for ≥6 consecutive months and either ongoing at Screening or stopped or paused ≥12 months before Screening

Key Exclusion Criteria:

- Suspected or confirmed disease or condition that may confound assessment of symptom-based clinical response, for example:
  - Radiographic presence of any cavity >5.0 cm internal diameter
  - Cystic fibrosis or other inherited disorders of airway ciliary dysfunction
  - Active allergic bronchopulmonary mycosis
  - Anticipated or planned lung surgery for treatment of MAC-LD
  - Disseminated MAC infection, or other known or suspected non-pulmonary source of infection requiring non-study antimicrobial therapy
  - Concomitant pulmonary infection requiring antimicrobial therapy
- Hgb <10.0 g/dL or <6.2 mmol/L at Screening; donation of blood or plasma or symptomatic loss of blood or hemorrhage within 28 days prior to randomization
- Severe hemoptysis within 28 days prior to randomization
- Immunodeficiency or an immunocompromised condition and risk for an opportunistic pulmonary infection

Analysis Populations

- Intent-to-Treat (ITT) Population: All randomized patients
- Safety Population: Randomized patients who received any study drug
- Micro-ITT Population: Patients who met the definition for the ITT Population and had MAC culture-positive respiratory specimens; primary efficacy endpoint analyses were performed in this population
- Per-Protocol Population: Patients who met the definition for the ITT Population and had no important protocol deviations that would affect the assessment of the primary efficacy outcome

Primary Endpoints – Phase 2

- Assessment of $MACrO_2$ PRO instrument psychometric properties, including assessment of symptom-based clinical response between baseline and Month 3, and baseline and Month 6, defined as improvement of ≥1 grade in the key symptom with no worsening of other symptoms, in the Micro-ITT Population (in the US)
- By-subject sputum conversion monthly through Month 6 in the Micro-ITT Population, based on 3 consecutive monthly negative sputum cultures for MAC (outside the US)
- Assessment of safety
  - TEAEs, SAEs, lab parameters, ECGs, and vital signs, including AEs of special interest (i.e., GI intolerance and anemia)

Secondary Endpoints – Phase 2

- SCC by Month 6 (key secondary endpoint in the US)
- Assessment of $MACrO_2$ PRO (key secondary endpoint outside the US)
- By-subject microbiological improvement at Month 3 and Month 6 in the Micro ITT Population, using decrease in MAC colony counts of ≥1 category
- PRO symptom/function-based clinical response in the Micro-ITT and Per-Protocol populations
  - Mean changes in PRO domain scores (e.g., QOL-B, NTM Symptoms Module, SGRQ-C)
  - Improvement of ≥1 grade in the key symptom with no worsening of other symptoms in the $MACrO_2$ PRO, monthly through Month 6

Key Statistical Methods

- Estimate the effect of treatment on PRO symptom/function-based responses, microbiological improvement and microbiological sputum culture conversion
- Psychometric analyses to identify the most appropriate threshold for the individual $MACrO_2$ PRO instrument items

SUMMARY

- Global, double-blind, operationally seamless study randomizing ~80 adults in Phase 2 with TR-MAC-LD to either EBO or PBO on top of an investigator-determined background regimen
- The data from the Phase 2 study were to inform selection of the primary outcome measure in Phase 3 and final targeted sample size

† Main/presenting author
‡ Author contributions made while affiliated with AN2 Therapeutics, but author may no longer be affiliated with the organization

CONFLICTS OF INTEREST:
- DMB is a paid consultant to the pharmaceutical industry, including AN2 Therapeutics.

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