Epetraborole: A Novel, Oral Antibiotic for NTM Lung Disease

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AN2 Therapeutics is a clinical-stage biopharmaceutical company developing treatments for rare, chronic, and serious infectious diseases with high unmet needs.

- Boron chemistry platform is driving a pipeline of anti-infectives
- **Epetraborole** is late-stage compound for NTM lung disease
- QIDP, Fast Track, and Orphan Drug designations granted in U.S.
- **Characteristics that favor development for NTM treatment**
  - Novel mechanism of action
  - Broad-spectrum antimycobacterial activity
  - Convenient, once-daily oral dosing
  - Superior microbiological efficacy compared to standard-of-care combination regimen in preclinical NTM animal models
  - Multiple Phase 1 studies out to 28-day dosing support well-tolerated dose and high probability of target attainment
- **Phase 2/3 pivotal trial in treatment-refractory Mycobacterium avium complex (MAC) lung disease currently enrolling** ([ClinicalTrials.gov Identifier NCT05327803](https://clinicaltrials.gov/ct2/show/NCT05327803))

NTM = Nontuberculous mycobacteria.
**Initial Epetraborole Pipeline** targets high unmet needs in rare, chronic and serious infectious diseases

*Boron chemistry approach enables targeting of novel biological targets*

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2/3</th>
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<tbody>
<tr>
<td>NTM LUNG DISEASE</td>
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<tr>
<td>Treatment-refractory MAC</td>
<td>US + Global</td>
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<td>Treatment-naïve MAC</td>
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<td><em>M. abscessus</em></td>
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<td>GLOBAL HEALTH</td>
<td></td>
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<td>Melioidosis (IV formulation)</td>
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MAC = *Mycobacterium avium* complex; NTM = Nontuberculous mycobacteria.
NTM lung disease is a rare, chronic and progressive infectious disease

• Epetraborole is being developed initially for the most common type of NTM, *Mycobacterium avium* complex (MAC)\(^1\)
  
  – MAC causes ~80%\(^2\) of cases of NTM lung disease (currently includes 12 species, most common of which are *M. avium*, *M. intracellulare*, and *M. chimaera*)

• Symptoms similar to those associated with other chronic respiratory diseases (e.g., cough, sputum production, fatigue)

• May progress to fibrosis, permanent lung damage and respiratory failure\(^1,2,3\)

  – Women and 65+ age group most affected
  – 5-year mortality rate between 10-48%\(^4\)

• Our initial focus is the treatment-refractory MAC subpopulation

  – ~15,000 patients in the U.S. and ~21,000 in Japan\(^5\)
  – Highest unmet medical need, with limited or no treatment options

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3. Nontuberculous Mycobacteria Lung Disease, Rare Disease Database, National Organization for Rare Disorders webpage (last updated 2018).
5. Internal analysis 2022, AN2 Therapeutics, Inc.
Novel Mechanism of Action (MOA)

Epetraborole inhibits the protein synthesis enzyme leucyl-tRNA synthetase (LeuRS) by binding to the terminal adenosine ribose of tRNA$^{Leu}$ in the editing site.
Broad Antimycobacterial Activity

In vitro antimicrobial activity against 51 clinical isolates of MAC, with MICs between 0.25 to 8 μg/ml.

Poster #1712 (Sat, Oct 22, 12:15-1:30PM)

<table>
<thead>
<tr>
<th>MIC Range</th>
<th>Epetraborole (μg/ml)</th>
<th>Clarithromycin (μg/ml)</th>
<th>Amikacin (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>2</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>8</td>
<td>4</td>
<td>64</td>
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</tbody>
</table>

Unpublished Data from Michelle S. DeStefano and Michael H. Cynamon, Central New York Research Corporation Syracuse, NY, U.S.

- Antimicrobial activity of epetraborole, clarithromycin and amikacin against 51 isolates of MAC including 17 *M. intracellulare* isolates, 1 *M. avium* isolates, 3 *M. avium* complex isolates, 20 *M. avium* subsp. *hominissuis* isolates, and 10 *M. chimaera* isolates.

- Epetraborole is **active against clarithromycin- and amikacin-resistant isolates** (data on file).
Antibacterial activity in a chronic mouse model of MAC lung disease

Improved antibacterial activity of epetraborole at all doses, compared to the daily humanized clarithromycin dose of 250 mg/kg.

Poster #1704 (Sat, Oct 22, 12:15-1:30PM)
Epetraborole antibacterial activity in a chronic model of MAC lung disease in mice

Significant reductions in MAC CFU with EBO monotherapy; superior decreases with EBO + SoC regimen (clarithromycin, ethambutol, rifabutin) compared to SoC alone.

Poster #1704 (Sat, Oct 22, 12:15-1:30PM)
Study EBO-101: A 28-Day Phase 1b dose-ranging study of oral epetraborole supports 500 mg once-daily dose for patients with treatment-refractory MAC lung disease

Poster #1727 (Sat, Oct 22, 12:15-1:30PM)

- Well-tolerated
- No serious adverse events (SAEs) or deaths
- 92% TEAEs mild, no severe TEAEs — Mild upper GI TEAEs most common type
- Linear PK

- Results support further development of epetraborole in NTM lung disease
  - Data from this and 6 other Phase 1 studies combined into Population PK model
  - EBO-101 results used in combination with preclinical data to determine epetraborole oral dosage for Study EBO-301 Phase 2/3 pivotal trial

500 mg once-daily dose achieved exposures with high probability of PK/PD target attainment for treatment of MAC lung disease
Favorable Pharmacokinetics

Results from Phase 1 intrapulmonary PK trial showed ~5x higher EBO exposures in lung macrophages (site of NTM infection) than in plasma.

Therapeutic doses of epetraborole achieved in alveolar macrophages (AMs) at doses that are substantially lower than maximum tolerated dosage in previous trials.

• New FDA Guidance for Industry for developing drugs in MAC lung disease released September 2021

• Efficacy endpoints now require symptom-based clinical response using PRO tools
  • No fully validated PROs in pulmonary NTM
  • No existing, fit-for-purpose PROs
  • No harmonization of PROs across different Sponsors developing new treatments

• Microbiological endpoints (e.g., sputum culture conversion) are secondary

• AN2 is evaluating a novel PRO with the FDA (Divisions of Anti-infectives and Clinical Outcome Assessments)
Study EBO-301 ("MACrO2"): Phase 2/3 pivotal clinical trial in treatment-refractory MAC lung disease

Currently enrolling; see macro2study.com and ClinicalTrials.gov NCT05327803

### Phase 2 Part

- **Double-blind Treatment Period***
  - Epetraborole + OBR
  - Placebo + OBR
  - N=40
  - N=40

### Phase 3 Part

- **Double-blind Treatment Period***
  - Epetraborole + OBR
  - Placebo + OBR
  - N =~156 (TBD)
  - N =~78 (TBD)

* 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, consisting of at least 2 antimycobacterial agents; **TBD** = Final Phase 3 sample size to be determined based on Phase 2 data.
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Thank You!