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Results: Phase 2 Study (EBO-301) to Assess the Efficacy, Safety, and PK of Oral Epetraborole (EBO) 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 NTM
- Treatment options for treatment-refractory *Mycobacterium avium* complex lung disease (TR-MAC-LD) are limited and often poorly tolerated
- Epetraborole is a boron-containing inhibitor of bacterial LeuRS, which is an essential enzyme in protein synthesis
- AN2 Therapeutics has completed a Phase 2 trial that randomized TR-MAC-LD patients to EBO or placebo (PBO) on top of an investigator-specified optimized background regimen (OBR)
- The design of this study is presented in a companion poster; study outcomes are presented herein

RESULTS

Figure 1. Enrollment and Disposition

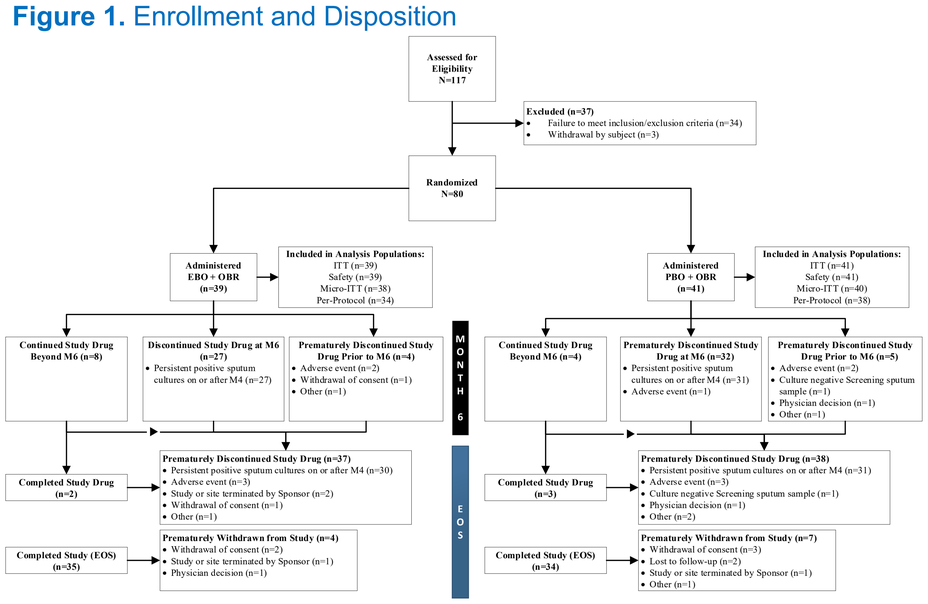


Table 1. Demographics and Baseline Characteristics Through Month 6

	EBO+OBR (N=39)	PBO+OBR (N=41)
Age, years Mean (SD)	64.7 (10.11)	64.7 (9.97)
Sex, n (%) Female	27 (69.2)	30 (73.2)
Race, n (%)		
Asian	26 (66.7)	25 (61.0)
White	13 (33.3)	15 (36.6)
Black or African American	0	1 (2.4)
Region, n (%)		
US	11 (28.2)	15 (36.6)
APAC	28 (71.8)	26 (63.4)
BMI <18.5 kg/m² at Baseline, n (%)	6 (15.4)	15 (36.6)
Predominant NTM Disease Classification, n (%)		
Non-cavitary nodular bronchiectatic	20 (51.3)	18 (43.9)
Cavitary nodular bronchiectatic	13 (33.3)	21 (51.2)
Fibrocavitary	6 (15.4)	2 (4.9)
Baseline Use of ALIS, n (%)	9 (23.1)	6 (14.6)
Time Since Initial MAC Diagnosis, years		
Mean (SD)	9.4 (6.07)	9.2 (5.84)
Median (min, max)	8.0 (<1, 22)	9.0 (1, 24)
Time Since First Diagnosis of Treatment Refractory Disease, years		
Mean (SD)	4.35 (4.364)	4.45 (4.088)
Median (min, max)	2.85 (0.2, 19.6)	3.25 (0.2, 14.6)
Underlying respiratory illness (e.g., bronchiectasis, COPD), n (%)	34 (87.2)	38 (92.7)

Table 2. Baseline OBR Through Month 6

Characteristic Statistic/Category	EBO+OBR (N=39) n (%)	PBO+OBR (N=41) n (%)
Number of Agents in Baseline OBR		
2	9 (23.1)	7 (17.1)
3	14 (35.9)	22 (53.7)
4+	16 (41.0)	12 (29.3)
Patients Initiating Any OBR Therapy at Screening	3 (7.7)	0 (0.0)
Baseline OBR Antibiotic Class		
Macrolide	30 (76.9)	35 (85.4)
Ethambutol	30 (76.9)	33 (80.5)
Rifamycin	28 (71.8)	30 (73.2)
ALIS	9 (23.1)	6 (14.6)
Non-liposomal amikacin	1 (2.6)	5 (12.2)
Clofazimine	11 (28.2)	10 (24.4)
Other	15 (38.5)	12 (39.3)
Most Common Unique Baseline OBR		
Ethambutol/macrolide/rifamycin	9 (23.1)	14 (34.1)
Ethambutol/macrolide	3 (7.7)	4 (9.8)
Ethambutol/macrolide/rifamycin/other	4 (10.3)	2 (4.9)

Table 3. Baseline Pathogens (Micro-ITT Population)

Pathogen	EBO + OBR (N=38) n (%)	PBO + OBR (N=40) n (%)
Mycobacterium avium	27 (71.1)	22 (55.0)
Mycobacterium intracellulare	11 (28.9)	21 (52.5)

- 3 patients in the PBO group had infection with both pathogens
- EBO MIC_{50} and MIC_{90} were 8 and 16 µg/mL, respectively, with an MIC range of 0.25 to >32 µg/mL
- 75.3% (61/81) and 90.1% (73/81) of isolates had EBO MIC of ≤8 and ≤16 µg/mL, respectively

Table 4. Baseline Pathogen Susceptibility to Selected OBR Agents (Micro-ITT Population)

	Baseline Pathogens from all Patients Combined (N=81)[a]					
	MIC (mg/L)			Interpretation, n (%)		
Antimicrobial	Range	MIC_{50}	MIC_{90}	S	I	R
Clarithromycin	≤0.25 - >32	4	>32	53 (65.4)	2 (2.5)	26 (32.1)
ALIS	4 - >128	64	>128	55 (67.9)	-	26 (32.1)
Amikacin (IV)	4 - >128	64	>128	15 (18.5)	16 (19.8)	50 (61.7)
Moxifloxacin	≤0.25 - >4	4	>4	21 (25.9)	19 (23.5)	41 (50.6)
Linezolid	4 - >16	>16	>16	9 (11.1)	17 (21.0)	55 (67.9)

[a] Baseline susceptibility profile for all antimicrobials was similar between treatment groups.

Table 5. Primary Endpoint (in US): $MACrO_2$ PRO Response Rate at Month 6 (Micro-ITT Population)

	EBO+OBR (N=38)	PBO+OBR (N=40)	Treatment Comparison		
Clinical Response	n (%)	n (%)	Difference (%)	95% CI	p-value
Response	15 (39.5)	10 (25.0)	13.9	(-6.8, 33.8)	0.1863
Failure	23 (60.5)	30 (75.0)	-	-	-

Table 6. Key Secondary Endpoint (in US): Sputum Culture Conversion by Month 6 (Micro-ITT Population)

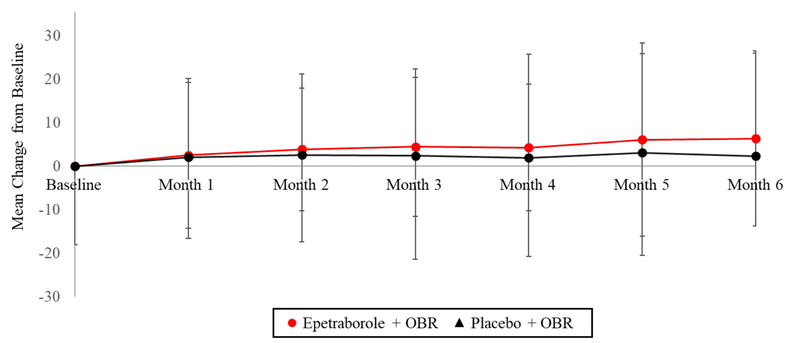
	EBO+OBR (N=38)	PBO+OBR (N=40)	Treatment Comparison		
Clinical Response	n (%)	n (%)	Difference (%)	95% CI	p-value
Response	5 (13.2)	4 (10.0)	3.4	(-12.0, 19.8)	0.6366
Failure	33 (86.8)	36 (90.0)	-	-	-

- Serial MIC testing (maximum tested EBO MIC value >32 µg/mL) demonstrated substantial variability in MIC from baseline through all post-baseline isolates
- 20/78 (25.6%) patients had a post-baseline isolate with a ≥4-fold increase in EBO MIC
- However, 11 of these 20 isolates (4/38 EBO and 7/40 PBO) had a subsequent MAC isolate with an EBO MIC within 2-fold of the MIC of the baseline isolate
- At Month 6 of treatment, all but 2 patients (1 EBO; 1 PBO) with an on-treatment isolate with EBO MIC >32 µg/mL had a subsequent isolate with MIC <32 µg/mL
- Laboratory testing variability, transient shifts in MIC, and/or infection with multiple different MAC pathogens might explain these observations

Table 7. Secondary Endpoint: Change from Baseline in QOL-B Respiratory Symptoms Score at Month 6 (Micro-ITT Population)

	EBO+OBR (N=38)	PBO+OBR (N=40)	Treatment Comparison		
Statistic			Difference	95% CI	p-value
N	34	35	-	-	-
Least Squares Mean (SE)	7.20 (2.447)	0.30 (2.569)	6.90	(0.45, 13.36)	0.0365
95% CI	(2.31, 12.09)	(-4.83, 5.43)	-	-	-

Figure 2. QOL-B RD Score Change from Baseline Over Time



- Baseline is defined as the last entry recorded or updated by the patient on or prior to the first dose of study drug + 1 day (ePRO-specified close of window to further entry by patient)
- QOL-B RD scores range from 0 to 100 (higher scores indicate better HRQoL)

Table 8. Summary of TEAEs Through EOS (Safety Population)

Participants With at Least 1:	EBO+OBR (N=39) n (%)	PBO+OBR (N=41) n (%)
TEAE	37 (94.9)	35 (85.4)
Study drug-related TEAE	30 (76.9)	10 (24.4)
Treatment-emergent AESIs	27 (69.2)	5 (12.2)
Anemia/Hgb decline	22 (56.4)	0 (0.0)
GI intolerance	14 (35.9)	5 (12.2)
TEAE leading to premature discontinuation of study drug	3 (7.7)	3 (7.3)
TEAE by maximum severity		
Mild	17 (43.6)	16 (39.0)
Moderate	16 (41.0)	14 (34.1)
Severe	4 (10.3)	4 (9.8)
Life-threatening	0 (0.0)	1 (2.4)
Death	0 (0.0)	0 (0.0)
Study drug-related TEAEs by maximum severity		
Mild	18 (46.2)	7 (17.1)
Moderate	11 (28.2)	2 (4.9)
Severe	1 (2.6)	1 (2.4)
Life-threatening	0	0
Death	0	0
Treatment-emergent SAEs	4 (10.3)	9 (22.0)
Study drug-related TESAEs	1 (2.6)	1 (2.4)

Table 9. TEAEs in ≥10% EBO-Treated Patients Through EOS (Safety Population)

Preferred Term	EBO+OBR (N=39) n (%)	PBO+OBR (N=41) n (%)
Participants With at Least 1 TEAE	37 (94.9)	35 (85.4)
Anaemia	14 (35.9)	0
Dizziness	7 (17.9)	0
Haemoglobin decreased	5 (12.8)	0
Headache	4 (10.3)	6 (14.6)
COVID-19	4 (10.3)	5 (12.2)
Diarrhoea	4 (10.3)	3 (7.3)
Pyrexia	4 (10.3)	3 (7.3)
Back pain	4 (10.3)	2 (4.9)

- Anemia/Hgb decrease was the most frequently reported drug-related TEAE
- Hgb values declined gradually with stabilization by Month 3 during EBO treatment, and returned to or toward baseline values post-treatment
- Decreases in Hgb were generally monitorable, manageable, and tolerated in this elderly patient population with advanced MAC-LD and underlying chronic respiratory illness

Abbreviations: AESI=adverse event of special interest; ALIS=amikacin liposome inhalation suspension; APAC=Asia-Pacific; COPD=chronic obstructive pulmonary disease; EBO=epetraborole; EOS=End of Study; GI=gastrointestinal; Hgb=hemoglobin; HRQoL=health related quality of life; I=intermediate; OBR=optimized background regimen; MAC=*Mycobacterium avium*; M=month; MIC=minimum inhibitory concentration; Micro-ITT=Microbiological Intent-to-Treat; PBO=placebo; PRO=patient-reported outcome; QOL-B=Quality of Life Bronchiectasis; R=resistant; RD=respiratory domain; S=susceptible; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TR-MAC-LD=treatment-refractory *Mycobacterium avium* complex lung disease.

CONCLUSIONS

- This study enrolled patients with severe, advanced TR-MAC-LD, including high rates of cavitary disease and long duration of disease
  - Baseline antimicrobial resistance rates in both treatment arms were high, including 32.1% to macrolides and 32.1% to ALIS
- Clinical response rates for both the $MACrO_2$ and QOL-B RD PROs were higher in the EBO+OBR group,
- The QOL-B RD change from baseline to Month 6, as analyzed by the least squares mean method, achieved nominal statistically significant improvement in EBO+OBR vs. PBO+OBR treated patients (p=0.0365)
- Sputum culture conversion rates were low and similar between treatment arms
- EBO MIC testing of postbaseline MAC isolates in both study arms demonstrated high variability
  - Approximately 25% of patients had a post-baseline isolate with a ≥4-fold increase in EBO MIC
  - However, 4/38 EBO and 7/40 PBO patients had a subsequent MAC isolate with an EBO MIC within 2-fold of the MIC of the baseline isolate
  - Sustained EBO MICs >32 µg/mL were infrequent (1 EBO and 1 PBO)
- EBO was generally tolerated with few study drug discontinuations, study withdrawals, and SAEs
  - GI intolerance events were generally mild to moderate in severity and infrequently led to study drug discontinuation
  - As anticipated from preclinical and Phase 1 data, anemia/Hgb decrease was the most frequently reported drug-related TEAE
  - Hgb values declined gradually with stabilization by Month 3 during EBO administration, and returned to or toward baseline values post-treatment
  - Decreases in Hgb were generally monitorable, manageable, and tolerated in these chronically infected, older patients
- The preliminary efficacy signal seen with the $MACrO_2$ and the QOL-B RD PROs aligns with FDA's focus on the patient voice in evaluating treatment response in NTM-LD; however, the key secondary endpoint of SCC was not met
- Phase 3 analyses have prespecified the QOL-B RD PRO as the primary efficacy endpoint

† 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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