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A Phase 2 Trial Designed to Enhance Signal Detection in an Evaluation of Bezisterim (NE3107) for the Treatment of Neurological Symptoms of Long COVID

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BACKGROUND

- Recent epidemiological studies have identified Long COVID as a leading neurological condition in the United States. It affects an estimated 400 million individuals worldwide[1,2]
- Neurological symptoms of Long COVID, such as cognitive impairment (or "brain fog") and fatigue, can persist for years after SARS-CoV-2 infection, leading to significant disability, and have no approved treatments[2,3-6]
- Ongoing neuroinflammation may be a key driver mediated by a persistent viral reservoir, protracted glial activation, and/or proinflammatory signaling[4,7]
- SARS-CoV-2 Spike protein can persist long after infection in the periphery and the brain, and can promote inflammation, neuronal death, and cognitive dysfunction through the TLR4 signaling pathway[4,7]
- TLR4 signaling leads to activation of NF-κB and ERK, which in turn stimulate the secretion of inflammatory cytokines, including IL-1β, IL-6, and TNF-α[7]
- **Bezisterim (formerly NE3107), a derivative of DHEA, is an anti-inflammatory agent being developed for neurodegenerative diseases in which TLR-driven inflammation contributes to cognitive decline**
  - Inhibits both TLR4-induced signaling and inflammatory NF-κB signaling[8]
  - Is orally available, not immunosuppressive, and crosses the blood-brain barrier[8,9]
  - Has a favorable safety and tolerability profile to date[10,11]
  - Is in development for Parkinson's and Alzheimer's disease
- **The aim of this proof-of-concept study** is to evaluate the efficacy, safety, and tolerability of bezisterim in adult participants with Long COVID who are enriched for cognitive impairment and fatigue

METHODS

- ADDRESS-LC (NCT06847191; www.addresslc.com) is a phase 2, multicenter, double-blind, randomized, placebo-controlled, 16-week study currently enrolling 208 adults with neurological symptoms due to Long COVID (**Figure**)
- Eligibility is confirmed by an enrollment authorization committee
- Participants enriched for subjective cognitive impairment and subjective fatigue who meet the eligibility criteria will be randomized 1:1 to either 20-mg bezisterim or matching placebo twice daily for 12 weeks. This novel trial design includes:
  - **Pragmatic considerations** based on input from clinicians and patients
  - **An informed enrichment enrollment strategy** to increase the likelihood of signal detection
  - **Stratification of participants by symptom duration** (<2 years or ≥2 years) to address the potential development of refractory symptoms with prolonged symptom duration **and by age** (≥18 to ≤45 years or >45 to <65 years) to address the potential impact of age on cognition
  - **A bespoke Cogstate Cognitive Battery** to provide an objective assessment of the impact of bezisterim on neurocognitive domains affected by Long COVID

Key inclusion criteria[a]

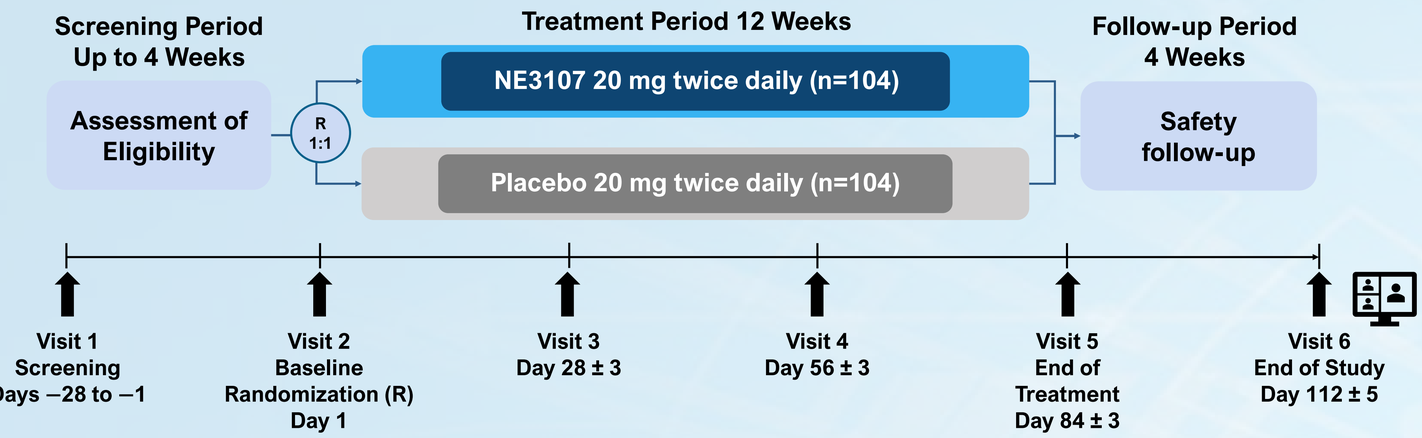
- Adult participants ≥18 to <65 years of age at screening
- Long COVID with neurological symptoms as defined below:
  - Current symptoms of **fatigue and neurocognitive impairment** that began or worsened after an index SARS-CoV-2 infection that occurred ≥3 months prior to screening
  - Index SARS-CoV-2 infection can be either a documented episode of COVID-19 with a positive test or a clinical diagnosis of COVID-19
  - Symptoms cannot be explained by an alternative diagnosis
  - Symptom duration of at least 3 months
- **PROMIS Cognitive Function Short Form 8a score ≤40[12]**
- **PROMIS Fatigue Short Form 13a T-score ≥60**
- Agree to maintain any other regular medications at current doses for the duration of the trial

Key exclusion criteria[a]

- Positive SARS-CoV-2 test in the past 30 days
- Received a vaccination for COVID-19 or influenza within 30 days of randomization
- Previous **admission to the ICU for COVID-19–related symptoms and/or if intubated** (ie, mechanical ventilation) for COVID-19 care
- Prior or active **unstable or progressive** major **psychiatric or neurological condition** that may impact ability to determine a treatment effect and is not related to SARS-CoV-2 infection as determined by the investigator
- Documented ADHD prior to index COVID-19 infection
- History of chronic fatigue syndrome, fibromyalgia, or POTS prior to index COVID-19 infection
- Currently taking or has received naltrexone within 30 days prior to first visit

[a]Note, this is not an exhaustive list for eligibility criteria.

ADDRESS-LC trial design: Double-blind, placebo-controlled, 12-week treatment period



5 visits to the doctor's office plus 1 virtual visit from home

Efficacy Objectives	Endpoints (Change at Week 12)
Objectively Measured Cognition	Bespoke Cogstate Cognition Battery (Change in overall/subdomain scores)
Psychomotor function	Detection Test
Attention	Identification Test
Sustained attention	Sustained Attention to Response Test
Processing speed	Digital Symbol Substitution Test
Verbal learning	International Shopping List Test
Verbal memory	International Shopping List Recall Test
Subjectively Measured Cognition	PROMIS Cognitive Function Short Form 8a
Fatigue	PROMIS Fatigue Short Form 13a
Sleep	PROMIS Sleep Disturbance Short Form 8a
Post-exertional malaise	DePaul Symptom Questionnaire, Post-Exertional Malaise[13]
Health-related quality of life	12-item Short Form Health Survey
Global impression of severity and change in symptoms	Participants Global Impression of Severity and Change • Overall impressions of change, Fatigue and Think clearly Clinician Global Impression of Severity and Change
Long COVID burdensome symptoms (frequency and severity) • Headache, Tinnitus, Decreased appetite	Long COVID Other Burdensome Symptoms Questionnaire
Long COVID Fatigue and Neurocognitive Symptom Exacerbations (incidence, severity and duration)	Long COVID Fatigue and Neurocognitive Symptom Exacerbation Questions

Safety Objective: Assess the effect of bezisterim on safety and tolerability using these endpoints

- **Incidence** and **severity** of treatment-emergent adverse events
- **Vital signs** (blood pressure, pulse, respiratory rate, and temperature)
- Clinically significant changes in 12-lead **electrocardiograms**
- Clinically significant changes in **clinical laboratory assessments** (hematology, chemistry, and urinalysis)
- Clinically significant changes in **physical examinations**

Exploratory Objective: Assess the effect of bezisterim on biomarkers using these endpoints

- Change in plasma biomarkers of **inflammation/immunity** over 12 weeks
- Change in plasma biomarkers of **neurodegeneration** and **metabolic dysfunction** over 12 weeks
- Change in biomarkers of **DNA methylation** over 12 weeks

CONCLUSION

- **This proof-of-concept study will provide important data on bezisterim as a treatment that may address multiple mechanisms leading to neuroinflammation resulting in cognitive dysfunction and fatigue associated with Long COVID**

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DISCLOSURES

PM, CR, CA, **JY,** and **JMP** are employees and shareholders of BioVie Inc. **CMP** is a consultant to BioVie Inc. and an employee of Biotechant Solutions LLC. **SOQ, MJP, LM, SH-YC**, and **IJK** have received consulting fees from BioVie Inc. **JMP** has the following patents approved or pending: BVIE.020WO, BVIE.028PR.

ADHD, attention-deficit/hyperactivity disorder; DHEA, dehydroepiandrosterone; ERK, extracellular signal-regulated kinase; ICU, intensive care unit; IL, interleukin; NF-κB, nuclear factor kappa B; POTS, postural orthostatic tachycardia syndrome; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation; SF, short form; R, randomization; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor alpha.

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