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A phase 1a single ascending dose study of the safety, tolerability, and brain receptor occupancy of BMS-984923 in healthy older adults

02.Clinical trials: results

Clinical Trial in Phase 1

Biographies (1 for poster/oral communications & 4 for the symposium) / 150 words per bio

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Abstract:

Background: Brain synapse loss in Alzheimer's disease (AD) has been tightly correlated with cognitive symptoms and developing drugs that preserve or restore synapses is an important therapeutic goal. Synaptic toxicity involves soluble Aβ oligomers (Aβo) binding to the cellular prion protein (PRPc) and metabotropic glutamate receptor subtype 5 (mGluR5) receptor complex. Multiple groups have shown that interrupting mGluR5 function rescues preclinical mouse AD phenotypes, making it an attractive drug target. However, mGluR5 has a physiological role as a glutamate receptor and full inhibition impairs function. We have identified a highly

potent and orally bioavailable mGluR5 silent allosteric modulator (SAM) , BMS-984923, that does not alter basal or glutamate activity, but does block Aβo/PrPC activation of mGluR5. In studies using multiple preclinical mouse AD models, treatment with BMS-984923 recovers synapse density, restores long term potentiation and returns memory performance to wild-type levels [1,2]. Preclinical animal studies have indicated low toxicity and high tolerability at proposed therapeutic doses, supporting the advancement of BMS-984923 to human studies.

Methods: Thirty-six participants between the ages of 50 to 80 years old with normal cognition were enrolled in an open-label, single ascending dose study. Six cohorts of 6 participants each were administered a single oral dose of BMS-984923 (10 mg, 40 mg, 70 mg, 100 mg, 150 mg, or 200 mg). Participants in each cohort were monitored for 7 days after receiving the study drug to assess safety and plasma drug exposure. A safety review was conducted at the completion of each cohort prior to escalation to the next dose cohort. For two participants each in the 10 mg, 40 mg, 70 mg, and 100 mg cohorts, three positron emission tomography (PET) scans with the mGluR5 radiotracer [^{18}F]FPEB were conducted off drug, and at approximately 4 and 24 hours post-dose. Distribution volume for each scan was estimated from dynamic scans with a metabolite-corrected input function using a 2-tissue compartment model. Receptor occupancy (RO) was derived from a graphical occupancy plot and related to BMS-984923 plasma concentration. A nonlinear least squares analysis was used to a fit a one parameter model and estimate IC_{50} with RO_{max} = 100%.

Results: All doses of BMS-984923 were well tolerated without serious adverse events. All treatment emergent adverse events (TEAEs) were mild or moderate in intensity and only 8 TEAEs were considered possibly related to treatment. Possibly related TEAEs consisted of 3 reports of brief oral sensations, 1 brief episode of dizziness, 2 reports of transient headache, 1 episode of transient hypertension, and 1 lab measurement of increased triglycerides. Plasma exposure increased linearly with increasing oral doses of BMS-984923. Based on the plasma concentration-RO model, the IC_{50} (SE) was 33.9 (4.0) ng/mL and IC_{80} (SE) = 135.7 (16.0) ng/mL.

Conclusion: BMS-984923 is safe and tolerable at single doses high enough to achieve significant target engagement, supporting continued development for the treatment of AD. Further studies are planned to assess the safety and tolerability of multiple doses of BMS-984923 in healthy older adults and patients with AD.

Keywords: BMS-984923, mGluR5, [^{18}F]FPEB, silent allosteric modulator

Clinical Trial Registry: NCT04805983, https://clinicaltrials.gov

Disclosures: TRS, SMS and Yale University have financial interest in Allyx Therapeutics, a company developing BMS-984923 for commercial use. Other authors do not have any conflicts of interest related to this study.

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