BPN14770, also known as zatolmilast, is a selective PDE4D negative allosteric modulator being developed for the treatment of FXS, Alzheimer's disease, and other cognitive disorders.

A **previous Phase 2a study in FXS** (adults males, n=30) comparing BPN14770 25 mg to placebo dosed twice daily showed:

- Statistically significant changes in performance-based and parent-rated scales on measures of communication and language
- A consistent advantage across diverse clinical domains (including cognitive and behavioral) on parent-rated, clinician-rated and performance measures
- BPN14770 was well-tolerated, with no serious or severe adverse events related to treatment.

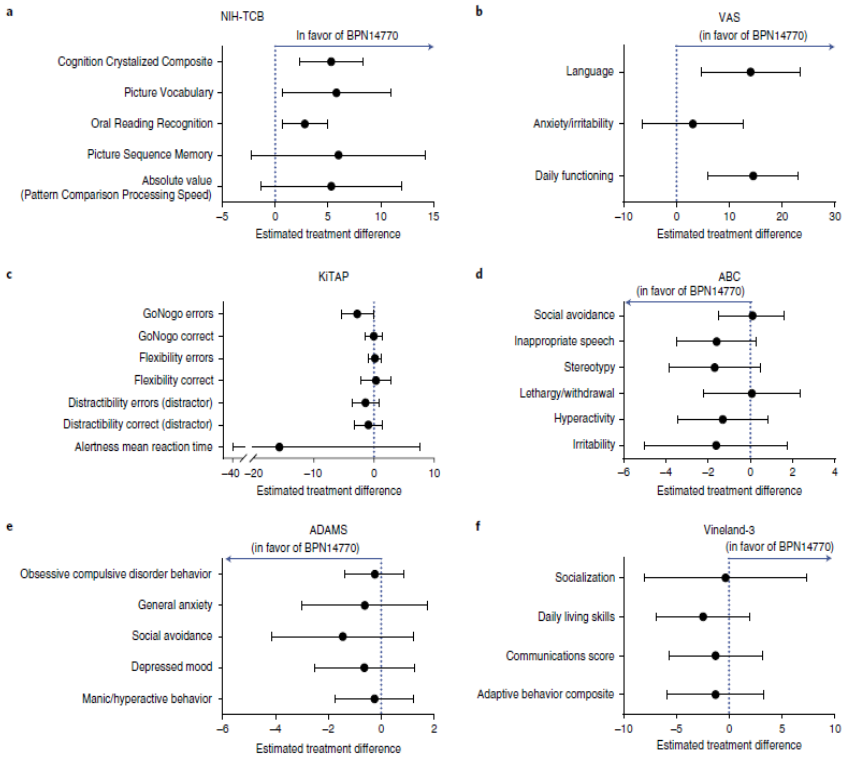


Fig. 1 | Forest plots of clinical outcomes. a–f, Forest plots for the clinical outcomes as assessed using the NIH-TCB (**a**), VAS parent/caregiver rating scales using patient-specific behavioral anchors (**b**), KiTAP (**c**), ABC (**d**), ADAMS (**e**) and Vineland-3 assessment of adaptive behaviors (**f**). Data are presented for period 1 only showing the LS mean difference (±95% CI) between BPN14770 and placebo on change from baseline through week 12 (n=15 BPN14770 and 15 placebo participants, except n=14 placebo participants for Vineland-3). The LS mean difference and 95% CI were obtained from the MMRM model and reflect the overall treatment effect during period 1 (including data from both weeks 6 and 12) from a model that included treatment, visit, predose baseline covariate and baseline Stanford-Binet full IQ score as fixed effects, with participant as a random effect.

From:Berry-Kravis EM, Harnett MD, Reines SA, et al. Inhibition of phosphodiesterase-4D in adults with fragile X syndrome: a randomized, placebo-controlled, phase 2 clinical trial. Nat Med. 2021;27(5):862-870. https://doi.org/10.1038/s41591-021-01321-w.

TETRA'S CURRENT FXS CLINICAL PROGRAM

BPN14770-CNS-204

- Adolescent males 12 to < 18 years
- Double-blind
- Randomized 2 active : 1 placebo
- 13 weeks treatment

BPN1477-CNS-301

- Adult males 18-45 years
- Double-blind
- Randomized 2 active : 1 placebo
- 13 weeks treatment

BPN14770-CNS-302

- 52-week open label extension
- Subjects who complete -204 or -301 through Week 13

Primary Eligibility Criteria

- FXS with a molecular genetic confirmation FMR1 >200 CGG repetitions.
- Current treatment with ≤ 3 psychotropic medications. Anti-epileptics don't count as psychotropic if used for treatment of seizures.
- Permitted psychotropic must be at a stable dose for at least 4 weeks prior to screening and must remain stable.
- Anti-epileptic medications must be at a stable dose for 12 weeks before screening and must remain stable.
- Subjects with a history of seizure currently receiving treatment must be seizure-free for 3 months prior to screening, or 2 years if not on treatment.
- Behavioral and non-pharmacological treatments must be stable for 4 weeks prior to screening and must remain stable.
- Subject must be willing to practice barrier methods of contraception or be abstinent.
- Must have consistent caregiver who can attend all visits.

Overview of Visit Schedules

BPN14770-CNS-204/-301 Double-Blind Studies

- Screening (14 to 28 days before Day 1)
- Day 1 - Baseline assessments
- Week 1- Telephone call
- Week 2 – Safety assessments
- Week 6 – Safety and Efficacy assessments
- Week 9 – Safety assessments
- Week 13 – Safety and Efficacy assessments
- Week 14 – follow up telephone call – *only if not going into BPN14770-CNS-302 Open Label Extension*

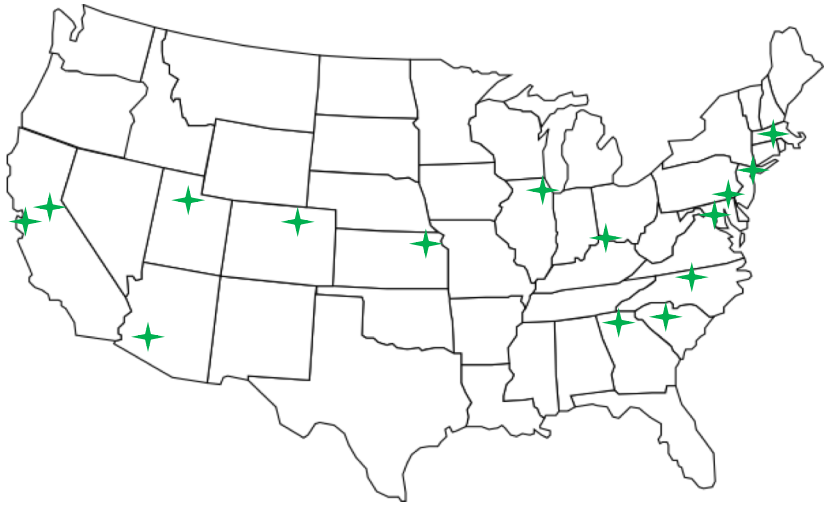
BPN14770-CNS-302 Open Label Extension

- Day 1 (same as Week 13 of -204/-301)
- Week 1- Telephone call
- Week 2 ,6, 9 – Safety assessments
- Week 12 Safety and Efficacy assessments
- Weeks 16, 20, 30, 42, 48 – Safety assessments
- Weeks 24, 36, 52 – Safety and Efficacy assessments
- Week 54 – Follow up telephone call

Screening and Day 1 visits and post-treatment visits to assess both safety and efficacy are expected to last 4-6 hours. Visits with only safety assessments are expected to last about 2 hours.

Other than routine blood draws, there are no invasive procedures or scans in these studies. Subjects will complete an IQ test at screening and a portion of the same test at later visits; subjects will also complete cognitive assessments on an iPad.

Caregivers will be asked to assess overall improvement, as well as specific improvement in daily living, language, academic skills (adolescents only) , and emotions/behaviors; caregivers will also be asked to complete the Vineland-3, ABC and ADAMS assessment tools.



Identified and Potential Clinical Sites

101 Rush Univ. Medical Ctr, IL (Berry-Kravis)
102 Cincinnati Children's Hosp, OH (Pedapati)
103 UC Davis Medical Center, CA (Hagerman)
104 Children's Hospital of Colorado (Tartaglia)
105 Kennedy Krieger Inst, MD (Budimirovic)
106 Seaver Autism Ctr, NY (Lozano, 301/302)
107 Barrow Neurological Institute, AZ (Frye)
108 UMass Medical School (Frazier)
109 Suburban Research Assoc,PA (Hatti)
110 Greenwood Genetic Center, SC (Buchanan)
112 Emory Univ. School of Medicine, GA (Talboy)
Univ of Utah: Primary Children's Hosp (Wilkins)
Univ of North Carolina Chapel Hill (Capal)
Univ of Kansas Medical Center (PI TBD)
Stanford University, CA (Reiss)

As clinical sites are activated in each trial, they will be listed on CilnicalTrials.gov.

Visit Tetra's website to find direct links to each study in ClinicalTrials.gov.

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