Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

BPN14770

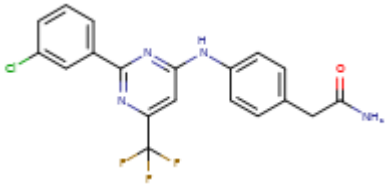
Evidence Summary

Potential cognitive enhancing properties at doses that don't cause nausea. Larger studies are needed to determine safety and efficacy for people with cognitive impairment.

Neuroprotective Benefit: May boost cognitive function in healthy adults. Could potentially aggravate tau pathology, so unclear if Alzheimer's disease patients will also benefit.

Aging and related health concerns: No studies have been done. Based on the target, BPN14770 is expected to be anti-inflammatory and could possibly help overcome cancer chemoresistance.

Safety: Well-tolerated without inducing nausea at low doses in short safety studies. Longer studies are needed.

Availability: Clinical trials	**Dose**: Not established (Range 5-30 mg/day projected based on Phase 1 RCTs).	**Chemical formula:** $C_{19}H_{14}ClF_3N_4O$ **MW**: 406.7936  Source: ChemIDplus
Half-life: ~10 hours	**BBB**: Penetrant	
Clinical trials: 3 Phase 1 RCT in Healthy adults (n=77, n=38, n=32).	**Observational studies**: None	

What is it? BPN14770 is a negative allosteric modulator of the phosphodiesterase 4 (PDE4) enzyme with preferential selectivity for the PDE4D isoform. It achieves this selectivity by binding to a phenylalanine residue in the N-terminal region of the PDE4 gene that is only found in the PDE4D isoform in primates [1]. In a mouse with a humanized version of the PDE4 gene, BPN14770 was 46-fold more potent, and 730-fold more selective towards PDE4D relative to PDE4B, the other major PDE4 isoform in the brain [1]. Since PDE4 is important for modulating the level and distribution of cAMP in the brain, its expression and activity levels can impact signaling processes involved in cognition. Non-isoform selective PDE4 inhibitors have shown cognitive enhancing properties, but were limited by emetic side effects [2]. Although PDE4D is the isoform associated with emesis, there are several (at least 9 in humans) variants of PDE4D, which differ in terms of functional properties and localization in the brain. The short form variants are the predominant forms expressed in the area postrema [3], the region of the brainstem that triggers emesis . Meanwhile, BPN14470 preferentially targets the long form variants [1], which are highly expressed in regions of the brain associated with learning and memory [3]. Therefore, BPN14770 is expected to be able to produce cognitive benefits at doses that do not induce emesis. BPN14770 is being developed for clinical testing by Tetra Discovery Partners Inc. It has been successfully tested for safety and tolerability in Phase 1 trials, and will be tested for cognitive enhancement in Alzheimer's disease and Fragile X Syndrome in upcoming Phase 2 trials.

Neuroprotective Benefit: May boost cognitive function in healthy adults. Could potentially aggravate tau pathology, so unclear if Alzheimer's disease patients will also benefit.

Types of evidence:

- 2 Phase 1 RCT (Healthy adults n=45, n=38)
- Several laboratory studies (2 for BPN14770)

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Cognitive function: Potential benefit

Non-isoform selective PDE4 inhibitors, such as rolipram, have been demonstrated to have cognitive enhancing and anti-depressant effects [2]. Since PDE4B and PDE4D are the dominant PDE4 isoforms in the brain, efforts have been made to determine which form is most important for mediating these effects. Although there are some discrepancies regarding whether 4D is involved in mediating the anti-depressant effects, rodent models using either isoform selective inhibitors or isoform selective knockdown using shRNA have demonstrated a role for PDE4D in cognition [4; 5; 6]. The isoforms are also processed into different isoenzymes with distinct N-terminal regions via alternative splicing. These isoenzymes are expressed in distinct spatial and temporal patterns, and have complementary, non-redundant roles [3]. Therefore, the functional effects of PDE4 inhibitors may depend not only on the isoforms targeted, but also on the isoenzymes within that isoform that are preferentially affected.

BPN14770 is 16-fold more potent toward the long-forms, which contain both regulatory upstream conserved regions (UCRs), compared to the short-forms, which lack one or both UCRs [1]. shRNA experiments in mice showed that the cognitive enhancing effects of rolipram could be recapitulated by selectively targeting the PDE4D long-form variants [4; 5]. In a Phase 1 RCT (NCT02840279) (n=45 over age 60), BPN14770 was found to improve cognitive function in cognitively normal older adults [7]. The cognitive boosting effects were limited to the low doses (10 and 20 mg). A post-hoc analysis of the low-dose groups (20 active + 10 placebo) revealed that BPN14770 treatment improved performance on a CogState working memory task. On the one-back test (ONB) there was an effect size of 0.5 to 5 ($P<0.05$-$P<0.01$), which is approximately equivalent to a 10% faster response time. A Phase 1 trial for BPN14770 in scopolamine-induced cognitive impairment in healthy adults (NCT03030105) (n=38) was completed in 2017, but the results have not been made public. Upcoming Phase 2 trials are expected to provide evidence toward whether it can produce clinically meaningful benefits in populations with cognitive impairment.

Human research to suggest benefits to patients with dementia: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Alzheimer's disease: Potential mixed benefit (preclinical)

Based on the cognitive boosting effects of non-selective PDE4 inhibitors in preclinical Alzheimer's disease (AD) models, and evidence supporting a role for long-form PDE4D isoenzymes in mediating the cognitive enhancing effects of these inhibitors, BPN14770 is projected to be beneficial for AD. However, the activation of cAMP in the frontal cortex appears to have a U-shaped dose response on working memory, suggesting that there is an optimal range for cognitive function [5]. While pro-cognitive in young monkeys, PDE4 inhibition by rolipram was found to produce cognitive deficits in aged monkeys [2]. This discrepancy has been attributed to the decline in PDE4 expression and increased cAMP/PKA signaling in the frontal cortex during aging in primates [8]. The dysregulation of Ca^{2+} signaling accompanying cAMP/PKA dysregulation is hypothesized to contribute to the development of amyloid beta and tau pathology in the aged primate dorsolateral prefrontal cortex (dlPFC) [9]. In young monkeys, PDE4D was found to be localized in dendritic spines in close proximity to microtubules, whereas these areas had reduced PDE4D and increased phosphorylated tau (pSer214) accumulation in the aged brain [10]. Inhibition of the PDE4D4 isoenzyme has been shown to promote the PKA-mediated phosphorylation of tau (pSer214), leading to microtubule reorganization [11]. The unique N-terminus of PDE4D4 allows it to interact with cytoskeletal localized SH3-domain containing proteins. In this way, PDE4D4 is hypothesized to preserve microtubule structures in the context of membrane-derived cAMP signaling [12]. This suggests that further inhibiting PDE4D4 could accelerate tau pathology. Since PDE4D4 is one of the long-form variants, it is expected to be preferentially affected by BPN14770. However, it is not entirely clear how the different PDE4D variants are specifically altered in the context of AD and/or general aging.

One small study comparing gene expression from the hippocampi of three healthy adults and one patient with severe AD found that while overall PDE4D levels were not changed, there was a general enrichment of short-forms and decreased expression of long-forms in AD [13]. Notably, the PDE4D4 variant was the only one not changed. While this suggests that long-form variants of PDE4D are already decreased in AD, it is not known whether this is a pathological or a compensatory response. Furthermore, as this study only involved one brain region in one AD patient, it is impossible to make conclusions about the generalizability of these findings. BPN14770 will be tested in early AD patients in an upcoming Phase 2 RCT (NCT03817684), but because the trial is focused on cognitive measures, it will not be able to determine whether it has an impact on reducing or aggravating tau pathology.

Fragile X syndrome: Potential benefit (preclinical)

Fragile X syndrome is a neurodevelopmental disorder that is characterized by a dysregulation of cAMP signaling and metabolism. Patients with Fragile X have intellectual disabilities and autism-like behaviors. BPN14770 (3 mg/kg/day orally for 2 weeks) was found to improve behavioral phenotypes in a mouse model of Fragile X (male *fmr1*-/-) [14]. This was accompanied by changes to dendritic spine density and maturation in the cortex. Notably, the behavioral improvements persisted following a two-week washout period, suggesting that the drug has long-lasting effects. However, the improvements did weaken over time, indicating that the changes were reversible, and continuous use would likely be necessary for sustained benefit in a clinical setting. BPN14770 will be tested in Fragile X patients in a Phase 2 RCT (NCT03569631).

Stroke: Unknown

Non-selective PDE inhibitors which have PDE4 inhibiting capacity have been used in the treatment of stroke, since PDE inhibition has vasodilatory effects, and can help prevent thrombosis. Increased PDE4 expression correlates with blood brain barrier (BBB) dysfunction in ischemic stroke, and preclinical models show that PDE4 inhibition can protect against BBB leakage [15]. However, SNPs in PDE4D, particularly rs702553, have been implicated in carotid atherosclerosis, atrial fibrillation, and stroke susceptibility [16]. PDE4D expression was found to be reduced on blood cells from stroke patients, suggesting that further PDE4D inhibition could exacerbate dysfunction. However, there is no direct evidence that PDE4D dysfunction plays a causative role in stroke, and it is not known how these risk-associated SNPs impact the expression level or activity level of the different PDE4D isoenzymes. Therefore, it is not known whether selective targeting of the PDE4D long-form isoenzymes would be protective, harmful, or neutral. Studies specifically testing BPN14770 in stroke models (with the humanized PDE4D gene) are needed.

APOE4 interactions: Unknown

Aging and related health concerns: No studies have been done. Based on the target, BPN14770 is expected to be anti-inflammatory and could possibly help overcome cancer chemoresistance.

Types of evidence:

- Several laboratory studies (None specifically for BPN14770)

Cancer: Unclear (as an adjunct therapy) (preclinical models)

Non-isoform selective PDE4 inhibitors, such as roflumilast (see Roflumilast report), have shown potential for reducing chemoresistance in cancer. Genetic studies of tumors have found that microdeletions in the regulatory UCR regions of PDE4D are common in a variety of tumor types. An immunohistochemistry analysis of 11 different tumor types (from 165 tumors) revealed that the tumors had elevated levels of PDE4D relative to surrounding healthy tissue [17]. The UCR regions allow for inhibition of the enzyme's activity through regulation by various kinases, such as ERK1. In UCR1 containing (long) forms, ERK1 activity inhibits PDE4D catalytic activity, while in (short) forms without UCR1, ERK1 activates PDE4D. The microdeletions then, in effect, lead to an overabundance of UCR1 lacking (short) forms that are activated by ERK1, which is generally elevated in cancer. In prostate cancer, expression of the PDE4D long-forms decrease with disease progression due to promoter methylation, leading to a shift toward more short forms [18]. In cell culture, cancer cells proliferated in response to treatment with a short form (PDE4D2), but not to a long form (PDE4D3) [17]. Elevated PDE4D has also been found to be associated with chemoresistance and be an indicator of poor prognosis [17; 19; 20; 21]. Rodent and cell culture systems indicate that non-selective or short-form PDE4D inhibition can help restore chemosensitivity and induce cancer cell growth arrest [17; 19; 22]. Since, BPN14770 preferentially targets long-forms of PDE4D, it is unclear whether it would be as effective. However, since specifically targeting the short-forms is expected to potentiate emesis, non-isoform selective PDE4D inhibitors may have a better therapeutic index.

Safety: Well-tolerated without inducing nausea at low doses in short safety studies. Longer studies are needed.

Types of evidence:

- 2 Phase 1 RCT (Healthy Adults n=32, n=77)
- 2 laboratory studies

BPN14770 targets the PDE4D isoform, which is the one associated with the emetic effects of PDE4 inhibitors. The emetic effects arise due to the expression of PDE4D in the area postrema of the brainstem. BPN14770 preferentially targets the long-form variants of PDE4D, and the brainstem primarily expresses the short-forms. Therefore, BPN14770 is only expected to induce emesis at high doses, which is supported by preclinical rodent studies and Phase 1 safety and tolerability RCTs [1; 7]. High doses (75 mg and 100 mg) for up to 8 days were associated with nausea and vomiting, but these

effects were not seen at lower doses (5 -20 mg), and overall the trials reported no increased overall incidence of gastrointestinal side effects [7]. Notably, it was only the low doses that showed cognitive benefits. BPN14770 was generally found to have a good pharmacokinetic profile with a high oral bioavailability of 70-80%. Larger, longer duration studies are needed to better assess the potential side effect profile, and to determine the populations at high risk for these side effects.

Sources and dosing:

BPN14770 is under clinical development by Tetra Discovery Partners Inc. The therapeutic dose has not yet been determined, but based on efficacy in rodent studies and a Phase 1 trial, it is expected to be between 5-30 mg/day [7].

Research underway:

Tetra recently entered a collaboration with Shionogi Inc. for the further development of BPN14770 in Fragile X and AD. In return, Shionogi has been granted the rights to market the drug in Asia, pending successful commercialization (Press release).

According to Clinicaltrials.gov, there are currently two active clinical trials for BPN14770.

It is being tested in a Phase 2 trial for patients with Fragile X syndrome (NCT03569631), which is estimated to be completed before the end of 2019. It is also being tested in Phase 2 trial for early AD patients (NCT03817684), which has an estimated completion date of June 2020.

Search terms:

Pubmed, Google: BPN14770 + Alzheimer's disease, dementia, cognition, cardiovascular, cancer, safety, clinical trials

Websites visited for BPN-14770:

- Clinicaltrials.gov
- Cafepharma

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