OGA Inhibition as a potential therapeutic approach for tauopathies: The PROSPER study, a phase II trial in PSP

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PSP Neuroscience Hub

Objective

- **To outline the therapeutic potential of OGA inhibition as a treatment for progressive supranuclear palsy (PSP).**
- **To describe the FNP-223 development program.**

Background

PSP is a primary tauopathy characterized by the pathological aggregation of Tau protein. It is distinguished by **ocular motor dysfunction**, **postural instability**, **akinesia**, and **cognitive dysfunction**.[1] No effective disease-modifying or neuroprotective therapy for PSP is yet available.[1]

OGA inhibition has been shown to elevate Tau O-GlcNAcylation and to impede the pathological aggregation of Tau[2]

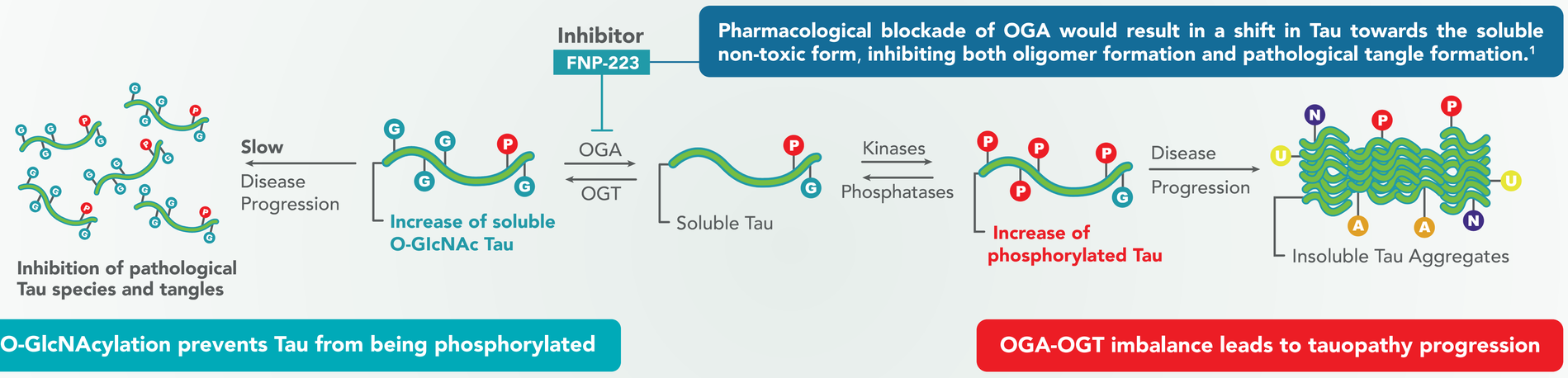

Figure 1. *FNP-223 mechanism of action.*

O-GlcNAcylation is a post-translational modification (PTM) of proteins that recently has emerged as a potential regulator of diverse cellular functions.[3] O-GlcNAcylation refers to the glycosylation of serine and threonine residues with O-GlcNAc monosaccharide (G) and it is exclusively regulated by 2 enzymes: OGA and OGT.[3] Under physiological conditions, there is a complex antagonistic cross-talk between glycosylation and phosphorylation.[4] Phosphorylation destabilizes Tau inducing protein aggregation.[4] O-GlcNAcylation may act as a protective layer against phosphorylation of different proteins like Tau.[4] Therefore, a new promising therapeutic approach for tauopathies is OGA inhibition.[5] *(Figure 1)*

FNP-223 is a new chemical oral compound that functions as a reversible and substrate-competitive inhibitor of the OGA, a new promising therapeutic approach for tauopathies such as PSP.[5]

FNP-223 is a novel OGA inhibitor positioned as a potential disease-modifying treatment for PSP

FNP-223 has proved therapeutic potential in preclinical models

Treatment with FNP-223 (formerly ASN90) in animal models has demonstrated to increase glycosylated Tau protein while decreasing Tau aggregates *(Figure 2 & 3)*, as well as improving survival and motor function *(Figure 4 & 5)*.[6] Preclinical studies have also shown a favorable safety profile.[6]

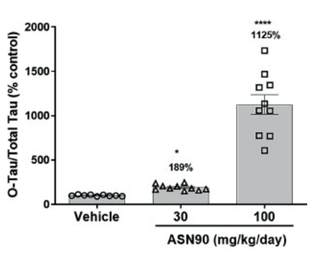

Figure 2. *O-Tau in the P30L mice treated for 4 days (steady state) with 30 and 100 mg/kg ASN90.*

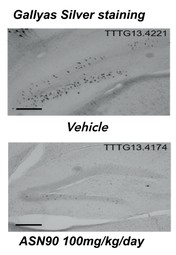

Figure 3. *NFT-like pathology in P301S Tau mice (3.5 months of treatment). 80% reduction of NFTs with ASN90.*

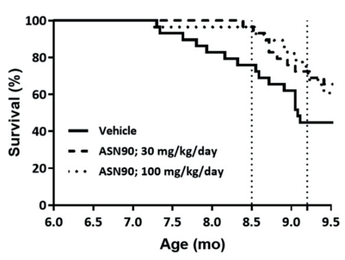

Figure 4. *Kaplan–Meier survival curves after chronic treatment of P301L mice with ASN90.*

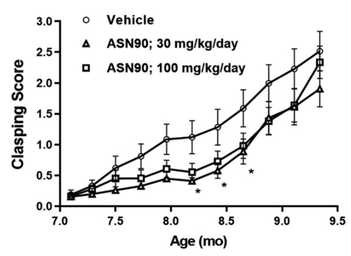

Figure 5. *Weekly clasping scores throughout chronic ASN90 treatment.*

FNP-223 in humans has demonstrated great OGA target engagement and excellent tolerability[6]

FNP-223 has also demonstrated favorable safety, PK and brain penetration in clinical phase I studies *(Figure 6 & 7)* and was well tolerated with no dose-limiting toxicities or serious adverse events.[4]

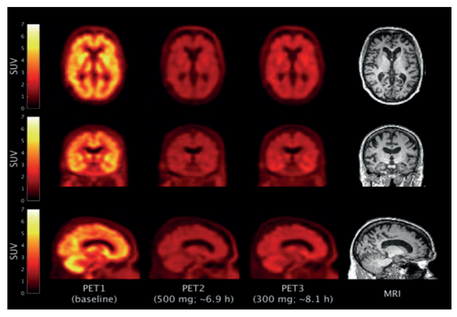

Figure 6. *Target engagement of ASN90 through PET imaging (ASN120290 PET Study). High binding of the [18F]-OGA inhibitor tracer throughout the human brain.[7]*

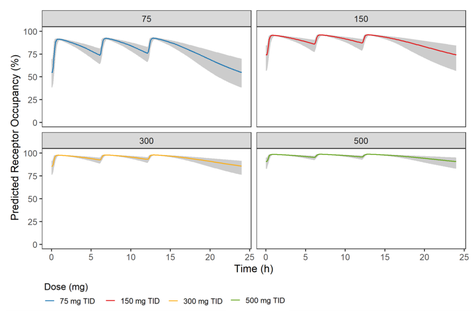

Figure 7. *PK/EO profiling in a human model. High CNS target engagement can be achieved with a well-tolerated dose of 300 mg TID.[8]*

PROSPER is a randomized, double-blind, placebo-controlled, phase 2 trial to assess the efficacy (slow disease progression), safety & tolerability of FNP-223 in the treatment of PSP.[9]

Study PROSPER
PROGRESSIVE SUPRANUCLEAR PALSY

Study Design

The PROSPER study will randomize 220 participants with PSP to FNP-223 (300 mg, oral, TID) or matched placebo in a 1:1 ratio. Participants will receive double-blind treatment for 52 weeks.

Study Start
May 2024 (Competitive Enrolment)

US (12 sites)
Spain (9 sites)
Germany (4 sites)
France (5 sites)
Italy (5 sites)
UK (4 sites)
Poland (2 sites)
Portugal (2 sites)
Hungary (1 site)

Study population

- Adult (50-80y) **possible and probable PSP-RS** (MDS 2017 criteria)
- Able to ambulate independently or with minimal assistance
- PSPRS score ≤40
  MoCA score ≥23
- PSP symptoms onset ≤3 years
- Study partner required along the trial

Selecting patients at the early stages of the disease works in conjunction with the mechanism of action to prevent the accumulation of Tau.

Endpoints

Primary endpoints to assess efficacy, safety & tolerability

- PSPRS change from baseline to 52w
- Incidence of TEAEs, SAEs, vital signs, laboratory evaluations, physical examinations and suicidal ideation/behavior (C-SSRS)

Secondary endpoints to assess disease severity functionality, cognition and QoL

Change baseline to 52w:

- Severity: CGI-S, PGI-S, CaGI-S
- Functionality: Slope of decline & subitems PSPRS, PSP-CDS
- Cognition: MoCA
- QoL: PSP-QoL, SE-ADL
- Pharmacokinetic (PK) characterization

Exploratory endpoints to assess brain volume changes, biomarkers of neurodegeneration and fall risk

Change baseline to 52w:

- Regional and whole brain volume changes: volumetric MRI (optional)
- Biomarkers: CSF (optional) & plasma
- Fall risk assessment: eDiary

Conclusions

FNP-223 is a promising disease-modifying therapy for PSP that is being studied to assess safety, tolerability, and efficacy in slowing disease progression in patients with PSP: the Phase 2 PROSPER study.

This poster is an encore presentation of data previously presented at the AD/PD 2025 Congress and the EAN 2025 Congress. Content has been updated where appropriate to reflect the most current information available.

C-SSRS: Columbia Suicide Severity Rating Scale; **CaGI-S:** Caregiver Global Impression of Severity scale; **CGI-S:** Clinical Global Impression of Severity scale; **CSF:** cerebrospinal fluid; **EO:** enzyme occupancy; **NFT:** neurofibrillary tangle; **MoCA:** Montreal Cognitive Assessment; **MRI:** magnetic resonance imaging; **OGA:** O-GlcNAcase; **OGT:** O-GlcNAc transferase; **PGI-S:** Patient Global Impression of Severity scale; **PK:** pharmacodynamic(s); **PSP:** Progressive Supranuclear Palsy; **PSP-CDS:** Progressive Supranuclear Palsy Clinical Deficits Scale; **PSP-QoL:** Progressive Supranuclear Palsy Quality of Life scale; **PSP-RS:** PSP Richardson Syndrome; **PSPRS:** Progressive Supranu-clear Palsy Rating Scale; **R:** Randomization; **SAE:** serious adverse event; **SE-ADL:** Schwab and England Activities of Daily Living Scale; **T:** telephonic visits; **TEAE:** treatment-emergent adverse event; **TID:** three times daily; **V:** in person visits.

REFERENCES: (1) Agarwal S, et al. Progressive Supranuclear Palsy. 2023 Mar 27. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. **(2)** Pratt MR, et al. Understanding and exploiting the roles of O-GlcNAc in neurodegenerative diseases. J Biol Chem. 2023 Dec;299(12):105411. **(3)** Alteen MG, et al. Monitoring and modulating O-GlcNAcylation: assays and inhibitors of O-GlcNAc processing enzymes. Curr Opin Struct Biol. 2021 Jun;68:157-165. **(4)** Ryan M, et al. Phase 1 study in healthy volunteers of the O-glcnacase inhibitor ASN120290 as a novel therapy for progressive supranuclear palsy and related tauopathies. Alzheimers Dement. 2018; 14(7):P251. **(5)** Yuzwa SA, et al. Increasing O-GlcNAc slows neurodegeneration and stabilizes tau against aggregation. Nat Chem Biol. 2012 Feb 26;8(4):393-9. **(6)** Permanne B, et al. O-GlcNAcase Inhibitor ASN90 is a Multimodal Drug Candidate for Tau and α-Synuclein Proteinopathies. ACS Chem Neurosci. 2022 Apr 20;13(8):1296-1314. **(7)** Oral communication: Dirk Beher, The Peter Davies Memorial Symposium: The Future of Tau Based Therapies. Alzheimer's Association International Conference, Denver, USA, July 26-30, 2021. **(8)** Oral communication: Dirk Beher, Translation of Tauopathy Therapeutics from Preclinical to Exploratory Clinical Trials Workshop. Rainwater Foundation. September 7 & 8, 2022; Washington, DC. **(9)** ClinicalTrials.gov: A Randomized, Double-blind, Placebo-controlled, Phase 2 Study to Assess the Efficacy, Safety, and Pharmacokinetics of FNP-223 (Oral Formulation) to Slow the Disease Progression of Progressive Supranuclear Palsy (PSP) (PROSPER). ClinicalTrials.gov [Internet]. Available at: https://www.clinicaltrials.gov/study/NCT06355531. Accessed on 30/01/2025.

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