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NIO752 in Progressive Supranuclear Palsy (PSP): Results of a Phase 1, Randomized, Placebo-Controlled Study

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Conflicts of interest: Günter U. Höglinger

	No, nothing to disclose
X	Yes, please specify

Company/name	Honoraria/ expense	Consulting/ advisory board	Funded research
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Alzprotect	X	X	
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Bayer	X	X	
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Biogen	X	X	
BMFTR			X
DFG			X
Ferrer	X	X	
Lilly		X	
Lundbeck	X	X	
Novartis	X		
Parkinson Stiftung			X
Rainwater Foundation			X
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Sanofi	X		
Teva	X	X	
UCB	X	X	X
Verum Stiftung			X
Zambon	X	X	

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Progressive supranuclear palsy (PSP)

- PSP is a rare, progressive, neurodegenerative tauopathy with no definitive known cause[1,2]
  - There are several different types of PSP, with Richardson's syndrome being most common[3]
  - PSP is characterized by insoluble 4-R tau deposits in the brain (neurons and tufted astrocytes), while CSF tau protein levels remain normal[1,2,4]
  - Contributing factors include genetic risk (in rare cases *MAPT* mutations), age, and environmental factors (eg, toxin exposure)[1,3,4]
- Despite having diagnostic criteria available, PSP is often misdiagnosed as Parkinson's disease[1,5-8]
  - ≈40% of patients with PSP are initially misdiagnosed[9]
  - Symptoms include postural instability with frequent falls, ocular motor impairment, and midbrain atrophy; symptoms most often do not respond to levodopa[5]
- There are no effective treatment options to slow or halt disease progression[1,3,10]
  - Symptom management involves medications for Parkinson's disease, fall prevention, antidepressants, glasses with bifocal or prism lenses, and physical, occupational, and/or speech therapy[6,10]

CSF, cerebrospinal fluid; MAPT, microtubule-associated protein tau; PSP, progressive supranuclear palsy.

1. Boxer A et al. *Lancet Neurol.* 2017;16(7):552-563. **2.** Stamelou M et al. *Nat Rev Neurol.* 2021;17(10):601-620. **3.** Ichikawa-Escamilla E et al. *IBRO Neurosci Rep*. 2024;16:598-608. **4.** Roemer SF et al. *Acta Neuropathol.* 2022;144(4):603-614. **5.** Krzosek P et al. *Front Aging Neurosci*. 2022;14:804385. **6.** National Institute of Neurological Disorders and Stroke. Progressive Supranuclear Palsy. Accessed January 27, 2026. https://www.ninds.nih.gov/sites/default/files/2025-05/progressive-supranuclear-palsy.pdf. **7.** Grimm MJ et al. *Mov Disord.* 2020;35(12):2301-2313. **8.** Respondek G et al. *Mov Disord.* 2020;35(1):171-176. **9.** Morgan JC et al. *J Neurol Sci*. 2021;421:117293. **10.** Rowe JB et al. *Pract Neurol*. 2021;21(5):376-383.

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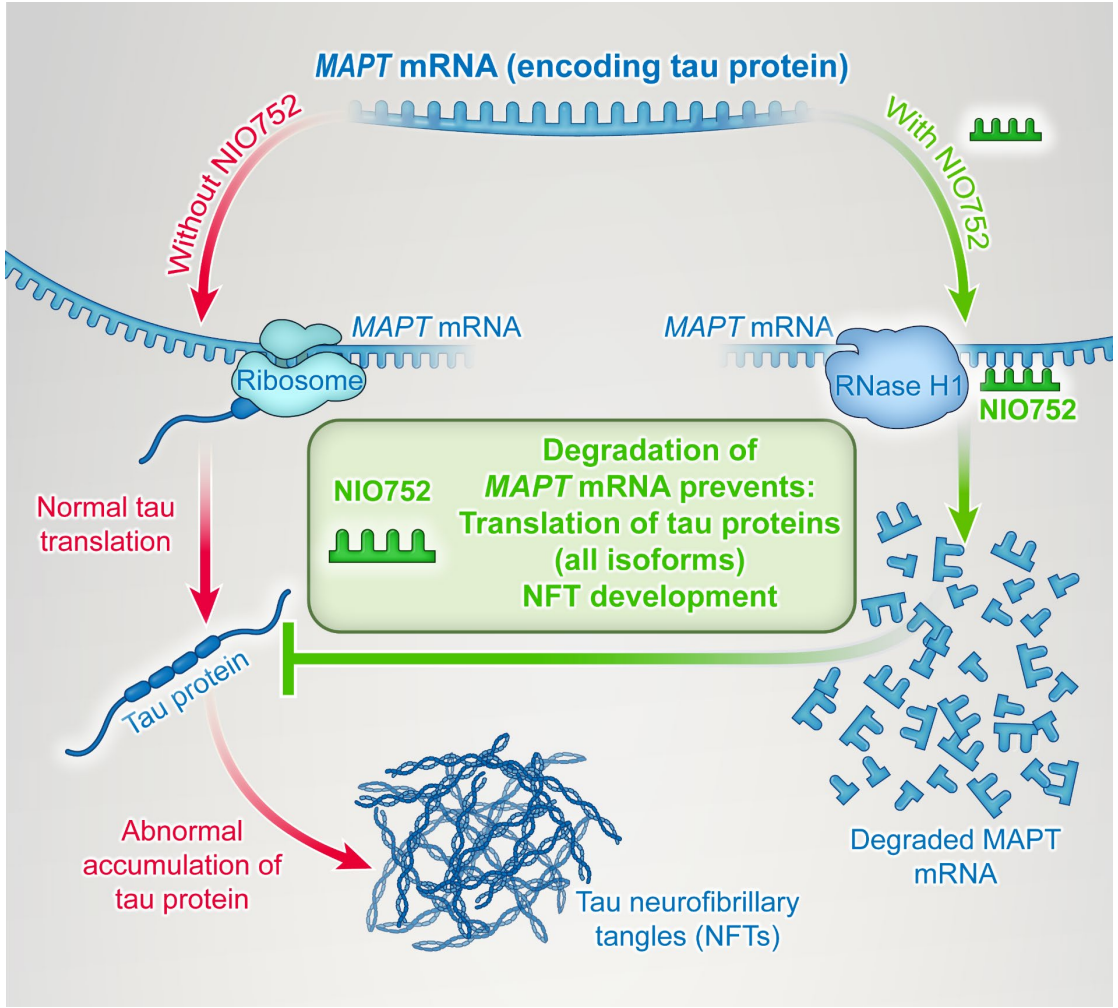
NIO752 mechanism of action

- NIO752 is an ASO that binds to *MAPT* mRNA, which encodes tau protein
  - NIO752 is the first *MAPT* ASO being studied in PSP
  - BIIB080, another *MAPT* ASO, has shown favorable results in mild Alzheimer's disease[1,2]
  - ASOs like NIO752 can act within both neurons and astrocytes[3,4]
- Binding of NIO752 to *MAPT* mRNA leads to recruitment of RNase H1, degrading mRNA
- Degradation of *MAPT* mRNA prevents production of tau protein and thereby may prevent accumulation of tau in NFTs and, potentially, pathology leading to PSP
- NIO752 targets all *MAPT* mRNA isoforms, enabling it to prevent production of all tau protein isoforms



ASO, antisense oligonucleotide; MAPT, microtubule-associated protein tau; mRNA, messenger RNA; NFT, neurofibrillary tangle; PSP, progressive supranuclear palsy; RNase, ribonuclease.

1. Shulman M et al. *Nat Aging.* 2026;6(2):445-453. **2.** Mummery CJ et al. *Nat Med*. 2023;29(6):1437-1447. **3.** Thirumalai S et al. *Alzheimers Dement.* 2025;21(1):e14560. **4.** Mortberg MA et al. *Nucleic Acids Res.* 2023;51(14):7109-7124.

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First-in-human, phase 1 study of NIO752

- We conducted a phase 1, multicenter, double-blind, placebo-controlled, multiple dose–escalation study of NIO752 in participants with PSP (NCT04539041)
  - Here, we present safety/tolerability, pharmacokinetic, and biomarker data from this study

Key eligibility criteria
- PSP diagnosis for <5 years
- Classified as probable PSP Richardson syndrome
- PSPRS-28 score <40 at screening
- MoCA score >17 at screening

Primary endpoint
- Safety and tolerability

Secondary endpoint
- PK parameters (plasma and CSF)

Exploratory endpoints
- Biomarkers of target engagement (total tau, p-tau181) and PD (NfL)
- Volumetric MRI assessments
- PSPRS-28 measures

CSF, cerebral spinal fluid; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; NfL, neurofilament light chain; PD, pharmacodynamics; PK, pharmacokinetics; PSP, progressive supranuclear palsy; PSPRS-28, 28-item Progressive Supranuclear Palsy Rating Scale; p-tau181, tau phosphorylated at threonine 181.

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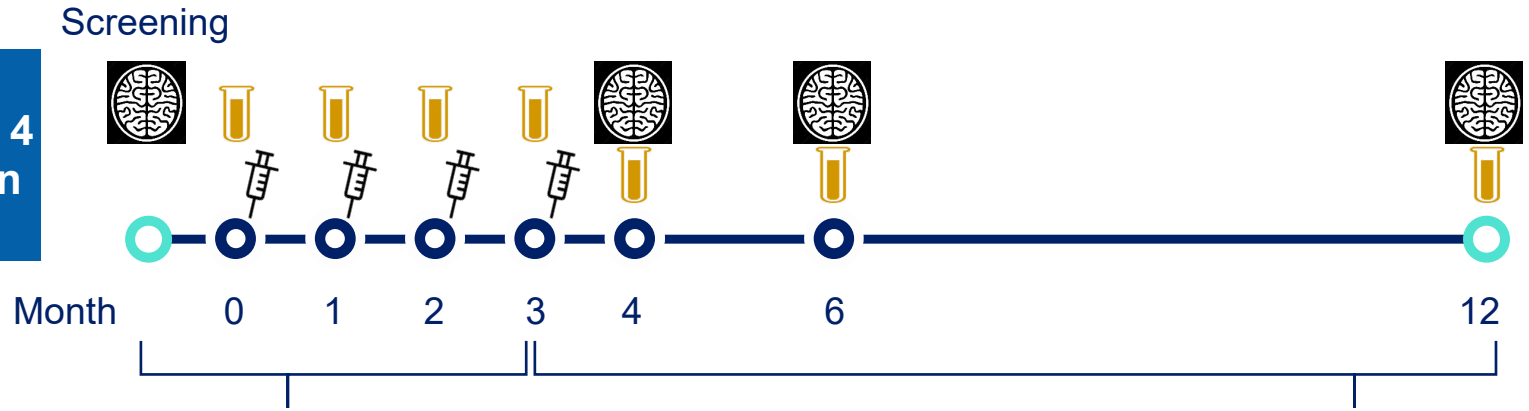
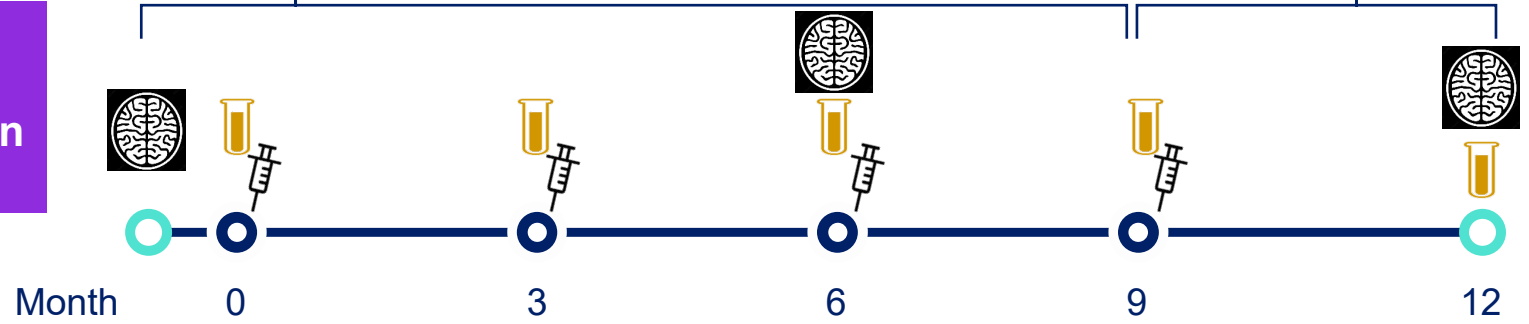
Participants were randomized to receive 4 intrathecal injections of NIO752 or placebo

Cohorts 1 to 4 study design



Cohort 5 study design



Cohort	n	Dose regimen
1	3	Dose A monthly (×4)
2	4	Dose B monthly (×4)
3	4	Dose C monthly (×4)
4	9	Dose D monthly (×4)
5	25	Dose D or C (×1) then dose C quarterly (×3)[a]

Doses escalated from A (lowest dose) through D (highest dose)

Legend

Intrathecal NIO752 | CSF and blood sampling | Volumetric MRI

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

[a] Cohort 5 initially received dose D (×1) followed by dose C quarterly (×3; cohort 5a [n=7]). After a per-protocol dose adjustment, further participants received dose C quarterly (×4; cohort 5b [n=18]).

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Disposition

- A total of 59 participants were enrolled (NIO752, n=45 [across 6 dose levels]; placebo, n=14) between February 2021 and October 2024
  - There were 12 sites in 4 countries (UK, USA, Canada, and Germany)

Participants, n (%)	NIO752 (n=45)						Pooled NIO752 (n=45)	Pooled placebo (n=14)
	Cohort 1 (n=3)	Cohort 2 (n=4)	Cohort 3 (n=4)	Cohort 4 (n=9)	Cohort 5a (n=7)[a]	Cohort 5b (n=18)[a]		
Started	3 (100)	4 (100)	4 (100)	9 (100)	7 (100)	18 (100)	45 (100)	14 (100)
Completed	3 (100)	4 (100)	4 (100)	8 (88.9)	5 (71.4)	14 (77.8)	38 (84.4)	11 (78.6)
Discontinued	–	–	–	1 (11.1)	2 (28.6)	4 (22.2)	7 (15.6)	3 (21.4)
Reasons for discontinuation								
Adverse event	–	–	–	–	1 (14.3)	1 (5.6)	2 (4.4)	–
Loss to follow-up	–	–	–	1 (11.1)	–	–	1 (2.2)	–
Patient decision	–	–	–	–	–	3 (16.7)	3 (6.7)	2 (14.3)
Death	–	–	–	–	1 (14.3)[b]	–	1 (2.2)[b]	1 (7.1)[b]

PSP, progressive supranuclear palsy.
[a] Cohort 5 initially received dose D (×1) followed by dose C quarterly (×3; cohort 5a). After a per-protocol dose adjustment, further participants received dose C quarterly (×4; cohort 5b).
[b] The 2 deaths (1 in the NIO752 group and 1 in the placebo group) were both assisted suicide and not suspected to be related to study treatment

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Enrollment was balanced in all cohorts

- At baseline, the overall median time since diagnosis was 1.6 years (range, 0.3-4.8 years)
- Overall median PSPRS score was 32.0 (range, 11.0-46.0),[a] and median MoCA score was 25.0 (range, 18.0-29.0)[b]

	NIO752 (n=45)						Pooled NIO752 (n=45)	Pooled placebo (n=14)
	Cohort 1 (n=3)	Cohort 2 (n=4)	Cohort 3 (n=4)	Cohort 4 (n=9)	Cohort 5a (n=7)	Cohort 5b (n=18)		
Age, mean (SD), years	69.0 (5.29)	64.5 (2.52)	65.3 (9.71)	66.1 (7.20)	65.3 (5.68)	64.9 (4.23)	65.5 (5.5)	67.4 (3.48)
Sex, female/male, n	1/2	3/1	2/2	5/4	1/6	9/9	21/24	7/7
Race, n (%)								
Asian	–	–	–	–	–	1 (5.6)	1 (2.2)	–
Black or African American	–	–	–	–	–	–	–	1 (7.1)
White	3 (100)	4 (100)	4 (100)	9 (100)	7 (100)	17 (94.4)	44 (97.8)	13 (92.9)
Time since diagnosis, median (range), years	1.3 (1.3-2.3)	1.9 (0.7-3.6)	1.9 (1.3-3.3)	0.9 (0.3-4.6)	1.4 (0.5-4.8)	1.8 (0.4-3.3)	1.5 (0.3-4.8)	2.0 (0.6-3.6)
PSPRS total score, median[a]	14.0	32.5	35.0	28.0	32.0	32.5	25.0	34.0
MoCA score, median[b]	26.0	24.0	26.5	24.0	25.0	25.5	31.0	23.5
CSF NfL level, median, pg/mL[c]	1980.0	1900.0	1602.0	1592.0	1199.0	1654.0	1592.0	1268.0
CSF total tau, median, pg/mL	243.0	234.0	349.0	185.0	182.0	213.0	211.0	246.0
CSF p-tau181, median, pg/mL	44.6	41.4	60.1	32.5	41.3	42.4	41.7	45.5

CSF, cerebrospinal fluid; MoCA, Montreal Cognitive Assessment; NfL, neurofilament lightchain; PSPRS, Progressive Supranuclear Palsy Rating Scale; p-tau181, tau phosphorylated at threonine 181.

[a] PSPRS: scores range from 0 to 100; high score correlates with more severe disease. [b] MoCA: scores range from 0 to 30; high score correlates with better cognitive function.

[c] Siemens Atellica assay.

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Serious AEs

- 2 fatal serious AEs (assisted suicide; 1 each with NIO752 and placebo) were reported
- Serious AE frequencies were similar to pooled placebo at dose D (cohorts 4 and 5a) and lower in other cohorts
- Overall, 15 of 45 participants (33.3%) receiving NIO752 and 7 of 14 (50.0%) receiving placebo reported serious AEs
  - 3 participants had treatment-related serious AEs, which led to dosage adjustments for subsequent participants
    - 2 cases of acute mental status changes with neurological symptoms, reported as encephalopathy
      - Event onset was within 12 hours after study treatment and spontaneously resolved in 2-4 days
    - 1 case of CSF pleocytosis (protein CSF, 52 mg/dL; leukocyte count, 32 cells/μL)[a] with no clinical signs and symptoms

	NIO752 (n=45)						Pooled NIO752 (n=45)	Pooled placebo (n=14)
Participants, n (%)	Cohort 1 (n=3)	Cohort 2 (n=4)	Cohort 3 (n=4)	Cohort 4 (n=9)	Cohort 5a (n=7)	Cohort 5b (n=18)		
Serious AE	1 (33.3)	–	1 (25.0)	5 (55.6)	3 (42.9)	5 (27.8)	15 (33.3)	7 (50.0)
Fatal serious AE	–	–	–	–	1 (14.3)	–	1 (2.2)	1 (7.1)
Treatment-related serious AEs								
Encephalopathy	–	–	–	1 (11.1)	1 (14.3)	–	2 (4.4)	–
Pleocytosis	–	–	–	–	–	1 (5.6)	1 (2.2)	–

AE, adverse event; CSF, cerebrospinal fluid.

[a] The serious AE of pleocytosis led to termination of dosing in the study; thus, the last 2 participants in cohort 5b did not receive their fourth dose.

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AE profile was consistent with the nature of PSP

- Treatment-emergent AEs were reported in 98.3% of participants; most AEs were mild (91.5%) to moderate (76.3%)
- Overall, the most frequently reported AEs were falls (44.1%), skin laceration (25.4%), and back pain (20.3%)
  - The frequencies of AEs were not dose dependent

Most frequent AEs by preferred term (reported in ≥15% of participants overall)

	NIO752 (n=45)							
Participants, n (%)	Cohort 1 (n=3)	Cohort 2 (n=4)	Cohort 3 (n=4)	Cohort 4 (n=9)	Cohort 5a (n=7)	Cohort 5b (n=18)	Pooled NIO752 (n=45)	Pooled placebo (n=14)
Fall	2 (66.7)	1 (25.0)	2 (50.0)	4 (44.4)	6 (85.7)	4 (22.2)	19 (42.2)	7 (50.0)
Skin laceration	1 (33.3)	2 (50.0)	1 (25.0)	4 (44.4)	–	5 (27.8)	13 (28.9)	1 (7.1)
Back pain	3 (100)	1 (25.0)	1 (25.0)	1 (11.1)	3 (42.9)	–	9 (20.0)	3 (21.4)
Skin abrasion	–	1 (25.0)	–	4 (44.4)	1 (14.3)	3 (16.7)	9 (20.0)	2 (14.3)
Hematoma	1 (33.3)	1 (25.0)	1 (25.0)	2 (22.2)	–	4 (22.2)	9 (20.0)	1 (7.1)
Gait disturbance	–	–	1 (25.0)	4 (44.4)	1 (14.3)	2 (11.1)	8 (17.8)	2 (14.3)
COVID-19	–	2 (50.0)	–	2 (22.2)	–	3 (16.7)	7 (15.6)	3 (21.4)
Contusion	–	–	–	3 (33.3)	–	4 (22.2)	7 (15.6)	2 (14.3)
Urinary tract infection	–	2 (50.0)	–	1 (11.1)	–	2 (11.1)	5 (11.1)	4 (28.6)

AE, adverse event; PSP, progressive supranuclear palsy.

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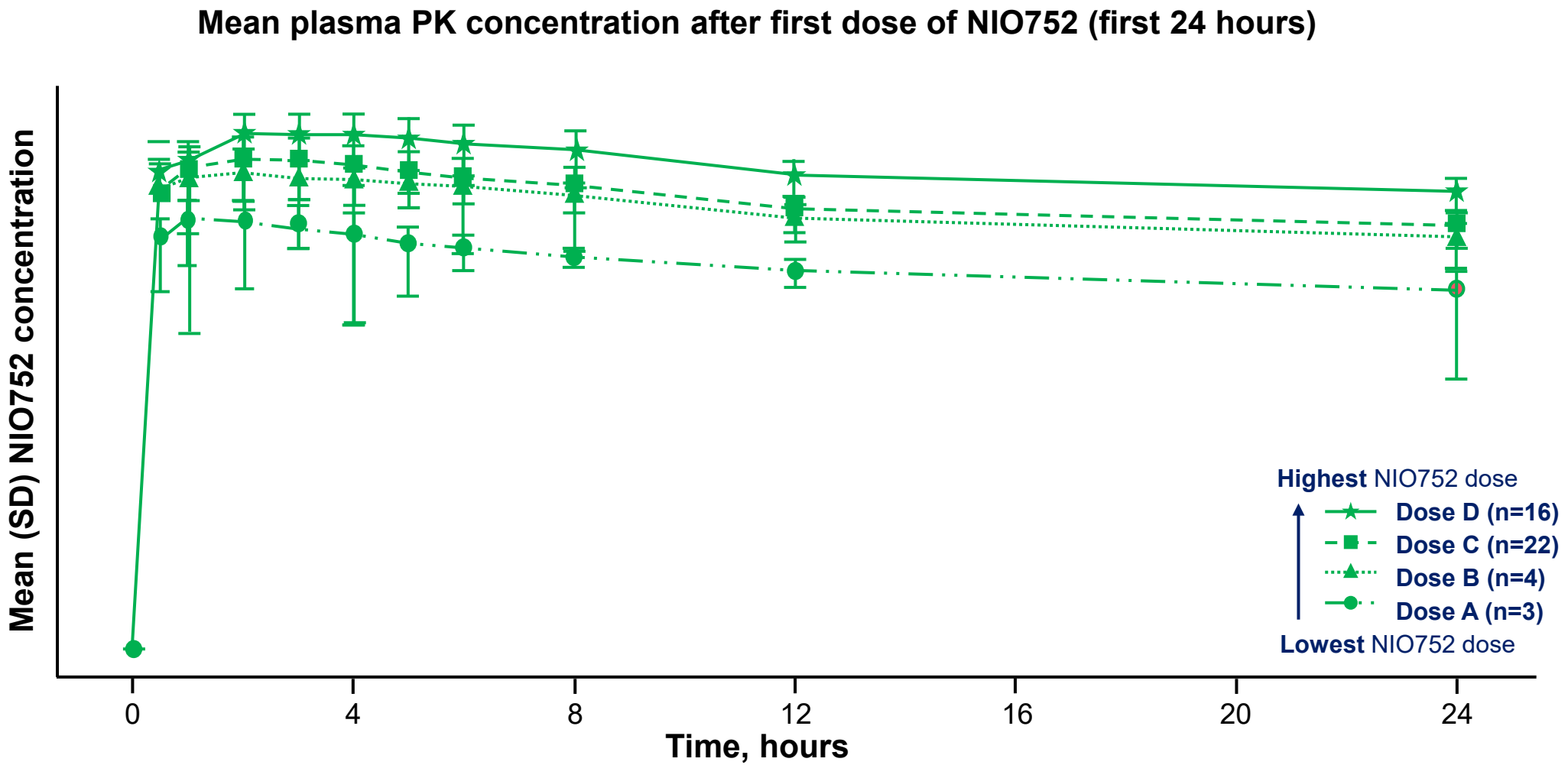
NIO752 exhibited dose-dependent exposure in plasma



PK, pharmacokinetics.

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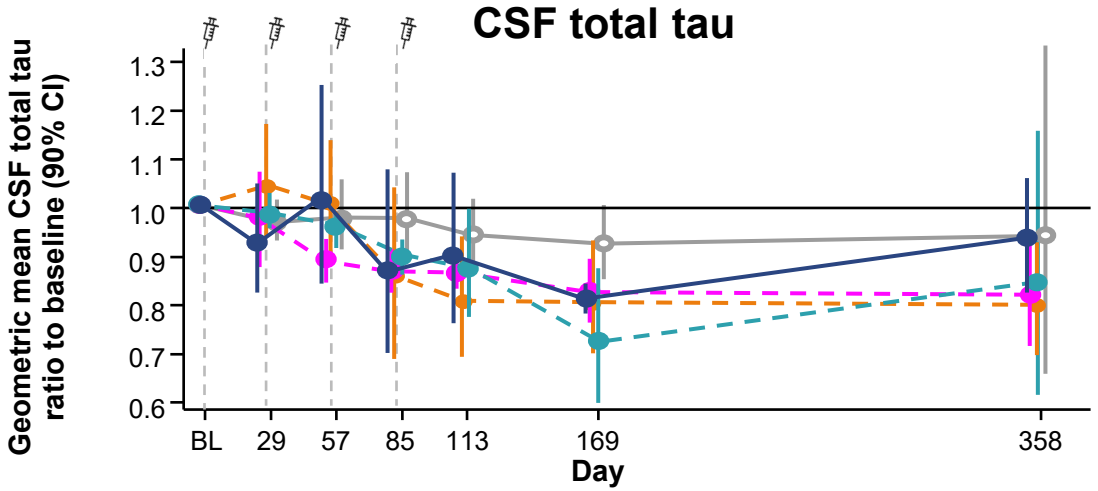
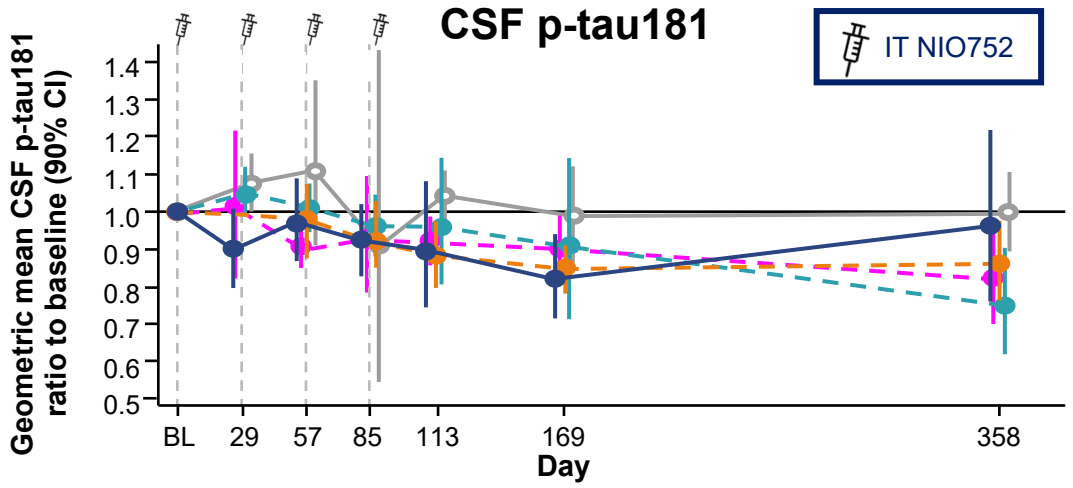
Target engagement was observed with NIO752 in cohorts 1 to 4

- Unlike in Alzheimer's disease, CSF tau levels are usually normal in people with PSP[1]
- In cohorts 1 to 4 (monthly dosing), there were decreases in CSF total tau and p-tau181 with NIO752 treatment
  - Response magnitude and duration were not dose proportional, possibly due to small sample sizes and/or sparse sampling

Cohorts 1 to 4





	BL	29	57	85	113	169	358
NIO752 cohort 1 (n=3)	3	3	3	3	3	3	3
NIO752 cohort 2 (n=4)	4	4	4	4	4	4	3
NIO752 cohort 3 (n=4)	3	4	4	4	4	3	3
NIO752 cohort 4 (n=9)	9	9	8	6	6	5	5
Placebo (n=6)[a]	6	3	3	6	5	3	

	BL	29	57	85	113	169	358
NIO752 cohort 1 (n=3)	3	3	3	3	3	3	3
NIO752 cohort 2 (n=4)	4	4	4	4	4	4	3
NIO752 cohort 3 (n=4)	3	4	4	4	4	3	3
NIO752 cohort 4 (n=9)	9	9	8	6	5	5	5
Placebo (n=6)[b]	6	3	4	6	5	5	4

BL, baseline; CSF, cerebrospinal fluid; IT, intrathecal; p-tau181, tau phosphorylated at threonine 181.

[a] Due to outlier values, 2 participants in the placebo group were excluded at day 57, and 3 participants in the placebo group were excluded at day 85. [b] Due to outlier values, 2 participants in the placebo group were excluded at day 57 and day 85.

1. Wagshal D et al. *J Neurol Neurosurg Psychiatry*. 2015;86:244-250).

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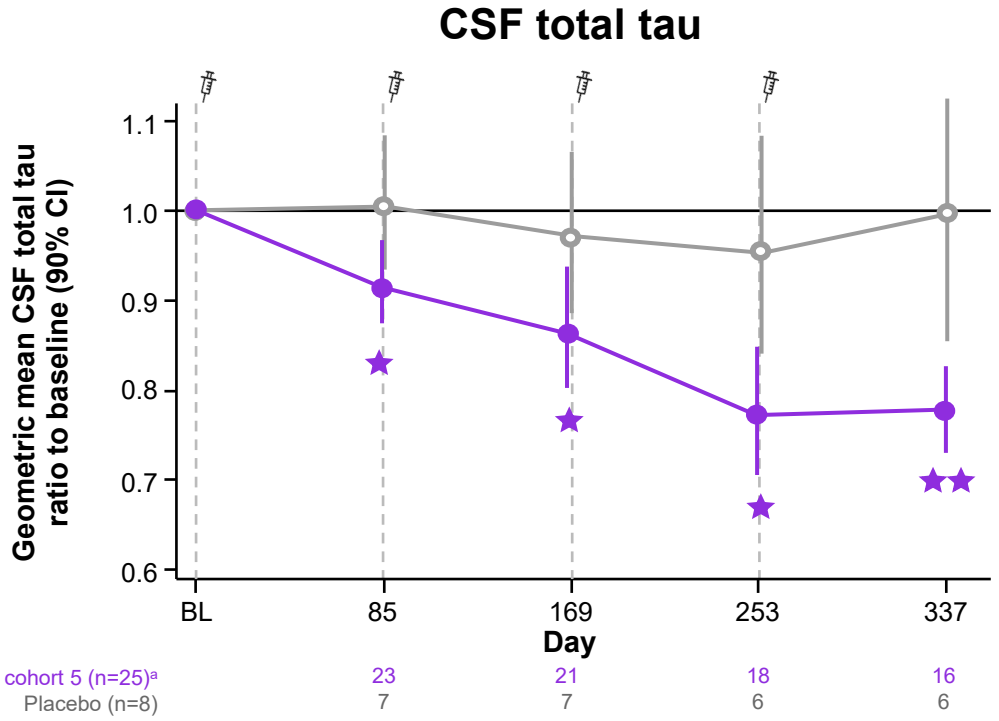
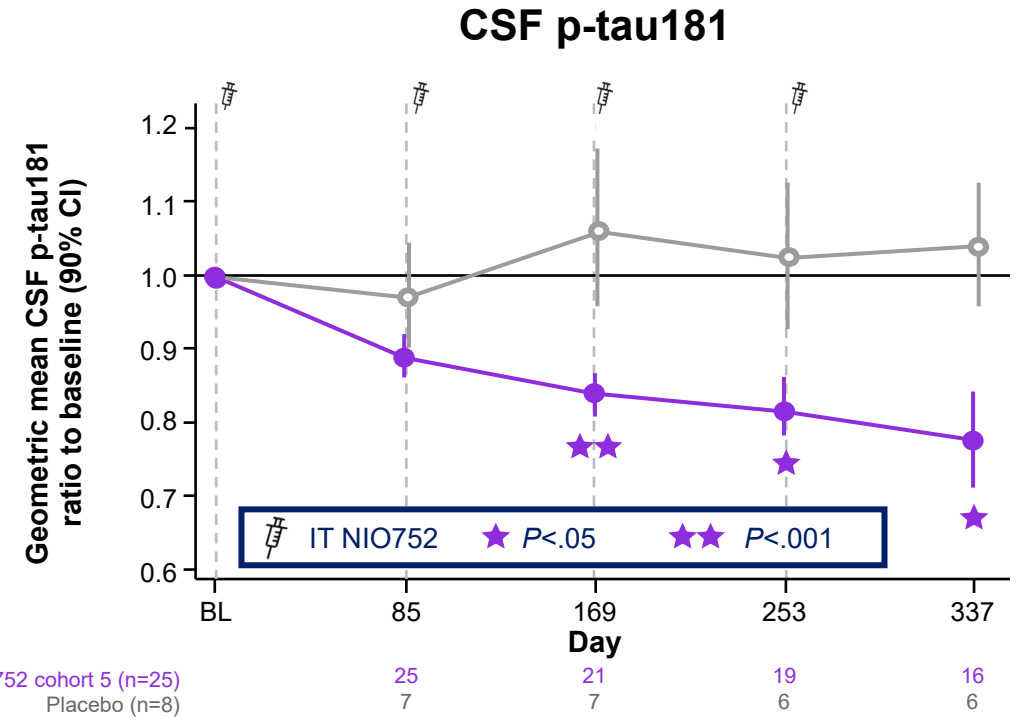
Target engagement was observed with NIO752 in cohort 5

- There were significant and sustained reductions in both CSF total tau and p-tau181 in cohort 5 with NIO752 (quarterly dosing)

Cohort 5





Statistical model: log-transformed ratios to baseline were analyzed using a MMRM model including treatment, visit, treatment by visit factors, and log-transformed baseline as covariates.
P values (NIO752 vs placebo) are 2-sided.
BL, baseline; CSF, cerebrospinal fluid; IT, intrathecal; MMRM, mixed model for repeated measures; p-tau181, tau phosphorylated at threonine 181.
[a] 1 participant in the NIO752 group was excluded at day 85 due to multiple head injuries.

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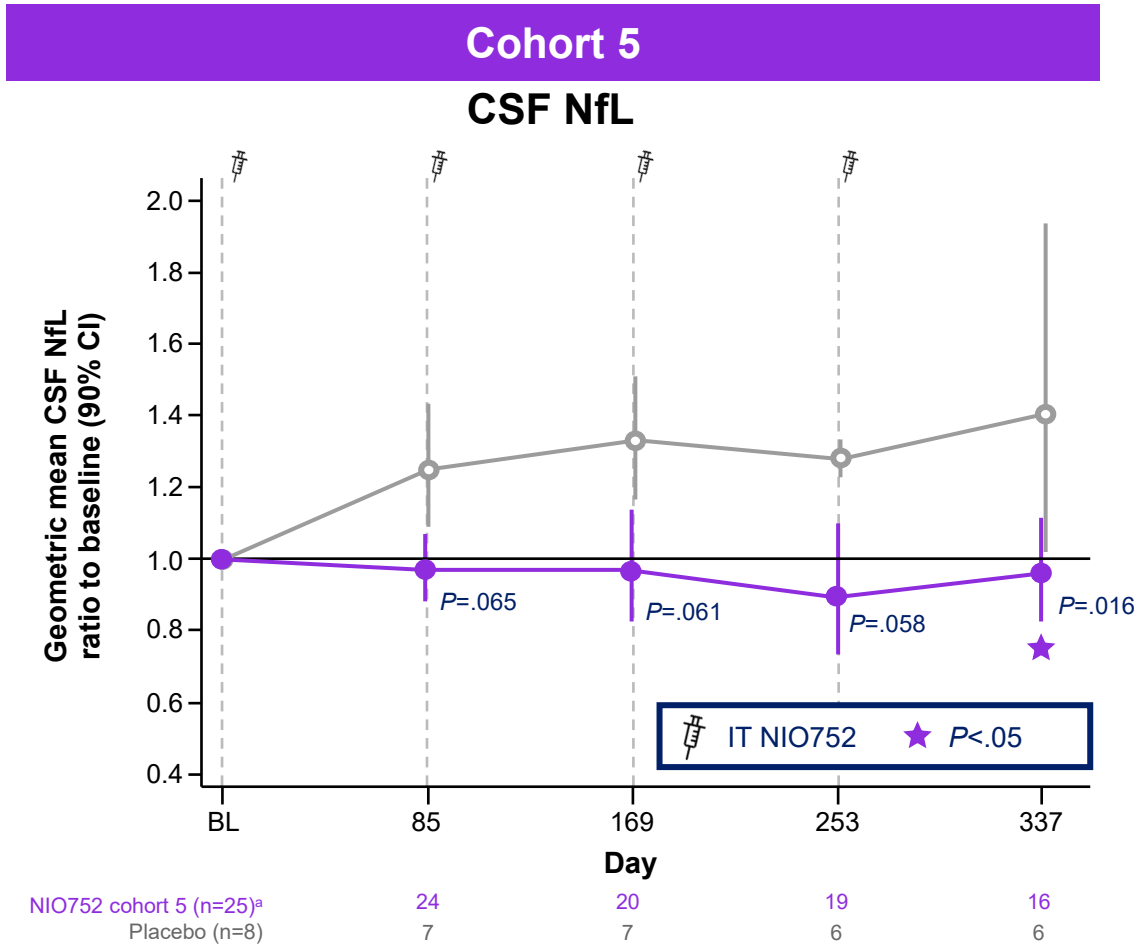
CSF NfL decrease vs placebo was observed in cohort 5

- NfL is a marker of neurodegeneration[1,2]
  - Elevated NfL levels are associated with disease progression in PSP[1,2]
  - NfL levels in PSP increase with disease progression by 10-29% per year[3-6]
- The mean CSF NfL level was unchanged from baseline in the cohort 5 NIO752-treated participants but increased with placebo, suggesting potentially beneficial downstream biological effect
  - Differences in CSF NfL level (NIO752 vs placebo) were observed, reaching significance at day 337 (estimated mean percent reduction vs placebo, 34%; *P*<.05)



Statistical model: log-transformed ratios to baseline were analyzed using a MMRM model including treatment, visit, treatment by visit factors, and log-transformed baseline as covariates.
P values (NIO752 vs placebo) are 2-sided.
BL, baseline; CSF, cerebrospinal fluid; IT, intrathecal; MMRM, mixed model for repeated measures; NfL, neurofilament light chain.
[a] 1 participant in the NIO752 group was excluded due to multiple head injuries.

1. Rojas JC et al. *Neurology*. 2018;90(4)e273-e281. **2.** Shapiro NL. *Brain Commun.* 2025;7:fcaf467. **3.** Rojas JC et al. *Ann Clin Transl Neurol.* 2016;3(3):216-225. **4.** Boxer AL et al. *Lancet Neurol.* 2014;13(7):676-85. **5.** Bäckström D et al. *Neurology*. 2020;95(7):e827-e838. **6.** VandeVrede L et al. *Mov Disord Clin Pract*. 2020;7(4):440-447.

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Conclusions

- NIO752 is the **first *MAPT* ASO** being studied in participants with PSP
- NIO752 demonstrated an **acceptable safety and tolerability profile** to move into further development
  - A few brief, transient cases of mental status changes with neurological symptoms reported as encephalopathy were observed with the highest dose
- There was **clear evidence of target engagement**, reflected by a reduction of CSF total tau and p-tau181 with NIO752 treatment
- CSF NfL level was unchanged from baseline with NIO752 compared with an increase with placebo in cohort 5, suggesting **potentially beneficial downstream biological effect**
- Together with the results presented here, preliminary analysis of clinical effects **support further clinical development** of NIO752 in this debilitating disorder
  - Exploratory analyses are ongoing and will be presented at a future meeting
- **The phase 3 PRESERVE trial** in PSP is being initiated

ASO, antisense oligonucleotide; CSF, cerebrospinal fluid; MAPT, microtubule-associated protein tau; NfL, neurofilament light chain; PSP, progressive supranuclear palsy; p-tau181, tau phosphorylated at threonine 181.

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Acknowledgments

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