# International Congress of Parkinson's Disease and Movement Disorders®
# 2025 Late-Breaking Abstracts

### LBA-1: Largest genotype-phenotype association study in Latin American cohorts highlights the role of ITPKB in Parkinson's Disease risk

*T.P. Leal; E. Waldo; F. Duarte-Zambrano; M. Inca-Martinez; J. Ramchandra; H.M. Chaparro-Solano; A.E. Anello; V. Borda; M.H. Gouveia; D. Teixeira-dos-Santos; P. Reyes-Pérez, E.M. Gatto; C. Perandones; M. Radrizzani; B.L. Santos-Lobato; G.L. Eufraseo; G.H. Letro; G. Arboled; O. Bernal-Pacheco; J. Orozco; B. Munoz; P. Chana-Cuevas; X.P. Corres; D. Aguillon; O. Buritica; G. Torrealba-Acosta G; M.V. Muller; C.M. Lopez-Razquin; P. Braga-Neto; R.M. Durón, M. Rodríguez-Violante; A.J. Hernández-Medrano; A. Cervantes-Arriaga; D. Martinez-Ramirez; A.F.S. Schuh, C.R.M. Rieder; M. Cornejo-Olivas; J. Rios-Pinto; A. Vinuela; V. Tumas; A.V. Pimentel; V. Borges; E.R. Barboso; C.L. Avila; P. Olguin; A. Colombo; J.C. Nunez; A. Medina-Rivera; A.E. Ruiz-Contreras; S. Alcauter; E. Dieguez; K. Nuytemans; Global Parkinson's Genetics Program (GP2); Latin American Research Consortium on the Genetics of Parkinson's Disease; I. Mata (Cleveland, OH, USA)*

### LBA-2: Interpretable deep learning framework for PSG-based classification of REM sleep behavior disorder and Parkinson's disease

*Y.J. Jung; S. Kim; J. Jeong (Seoul, South Korea)*

### LBA-3: Long-Term Efficacy and Safety of Omaveloxolone in Patients With Friedreich Ataxia: 4-Year Data From the Ongoing MOXIe Open-Label Extension

*T. Zesiewicz; D.R. Lynch; M.B. Delatycki; J.C. Hoyle; S. Boesch; W. Nachbauer; P. Giunti; G. Wilmot; S.H. Subramony; K.D. Mathews; S. Perlman; R. Lawson; C. Shen; S. Farooq; S. Natarajan; R.M. Domingo-Horne; A. Arizpe; N. Folschweiller; M. Murai (Tampa, FL, USA)*

### LBA-4: N-acetyl-L-leucine: Findings from the Extension Phase of a Phase II Clinical Trial in Ataxia-Telangiectasia

*M. Patterson; B. Zanrucha; J. Raymond; A. Hatcher; J. Kerthi; T. Fields; I. Billington; M. Strupp (Austin, TX, USA)*

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*E. Eitan; O. Volpert; S. Rau; A. Gekas (Natick, MA, USA)*

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*H. Mao; Y. Kuang (Guangzhou, Guangdong, People's Republic of China)*

### LBA-7: Vatiquinone Prevents Ferroptosis in Preclinical Models of Friedreich's Ataxia

*J.K. Trimmer; J.C. Latham; A. Minella; A. Krieger; A. Karcini; S. Chaudhary; Y.J. Kang; Y. Mao; M. Weetall; J.J. Cherry (Warren, NJ, USA)*

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*A. Patel; K. Patterson; D. Kholsa; R. DeGryse; N.Y. Huang; R. Dimitrova; M.C. Munin; P. McAllister; C.A. Cooper; D.M. Simpson; S.H. Isaacson; R. Pahwa; R.L. Barbano; L. James (Overland Park, KS, USA)*

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*D.V. Amrutkar; K. Sandager-Nielsen; T. Dyhring; T. Jacobsen; J. Larsen; P. Muglia; R. Hofbauer; S. Pathak; H. Lin (Glostrup, Hovedstaden, Denmark)*

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*I. Martinez-Valbuena; M. Abarghouei; D. Olszewska; M. Sousa; D. Di Luca; N.G. Reyes; S. Fereshtehnejad; C. Anastassiadis; J. Ta; J. Li; R. Cheung; J. Sasitharan; P. Bhakta; S.H. Fox; M.C. Tartaglia; G.G. Kovacs; A.E. Lang (Toronto, ON, Canada)*

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*R. Real; R. Fumi; D. Vaughan; Y. Kordovska; O. Swann; A. Heslegrave; H. Zetterberg; H. Morris (London, United Kingdom)*

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*R. Gregg; C. Christianson; K. Liu; T. Nguyen; R. Jucius; K. Ogilvie; B. Crean; J. Callahan; J. Nuss; M. Pomper; D. Russell; M. Forman (San Diego, CA, USA)*

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*H. Na; C.W. Park; K.W. Chang; M. Kim; D.H. Kim; S. Park. C.Y. Park; M.S. Kim; I. Jung; J.W. Chang; D.W. Kim; P.H. Lee (Seoul, South Korea)*

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*L. Jun; C. Yuejun; L. Dianyou; T. Yuyan; L. Ningdi; Z. Liche; F. Haiyan; Y. Shanzheng. G. Juanhong; W. Junfeng (Shanghai, People's Republic of China)*

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*W. Jost; F. Bergquist; A. Evans; S. Hassin-Baer; R. Hauser; T. Henriksen; I. Malaty; T. Mestre; P. Mir; R. Rodriguez; P. Schwingenschuh; M. Simu; L. Bergmann; R. Gupta; P. Kukreja; M. O'Meara; J.C. Parra; M. Shah; J. Aldred (Wolfach, Germany)*

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*D. Devos; P. Odou; J. Labreuche; G. Touzet; N. Reyns; A. Duhamel; C. Leclercq; T. Ouk; K. Dujardin; L. Carton; A. Rolland; D. Deplanque; V. Foutel; M. Fisichella; C. Moreau (Lille, Haute de France, France)*

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*R. Pahwa; R. Dhall; Z. Mari; A. Tarakad; C. Oehlwein; R. Sanchez; S. Duvvuri; I. Chang; J. Boiser; C. Zadikoff (Kansas City, KS, USA)*

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*Y. Kuang; H. Mao; P. Xu (Guangzhou, Guangdong, People's Republic of China)*

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*C. Xiong; H. Hang; H. De La Cruz; A. Avidon; D. Bliwise; M. Campbell; S. Criswell; A. Davis; K. Duff; K. Ehgoetz-Martens; J. Elliott; T. Ferman; J. Fields; L. Forsberg; J.F. Gagnon; Z. Gan-Or; M. Howell; M. Hu; X. Hu; D. Huddleston; K. Kantarci; P. Kotzbauer; J. Langley; M. Lim; J. Locke; V. Lowe; S. McCarter; J. McLeland; M. Miglis; E. Mignot; T. Miyagawa; L. Neilson; K. Nichols; A. Pelletier; O. Ross; C. Schenck; W. Singer; E. St. Louis; O. Sum-Ping; L.M. Trotti; A. Videnovic; Y. Ju; B. Boeve; R. Postuma (St. Louis, MO, USA)*

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*M. Biagioni; R. Nicholl; T. Bornemann; C. Legendre; S. Leach; H. Naik; A. el Baghdady; N. Williamson; A. Benoit; D. Menshykau; L. Vroye (Braine-l'Alleud, Walloon Brabant, Belgium)*

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*M. Cruz Rodríguez-Oroz; A. Dalvi; L. Zucker; W.C. Chang; P. Wu; M. Kaplitt; H. Sarva; H. Eisenberg; P. Fishman; V. Buch; M. Matarazzo; M. del Alamo; S. Sani; M. Pourfar; A. Mogilner (Pamplona, Spain)*

**LBA-22: First Clinical Trials of ARV-102, a PROTAC LRRK2 Degrader: Characterization of Pathway Engagement in Healthy Volunteers and Patients With Parkinson's Disease**

*L. Smits; C. Woodward; S. Aksenov; A.L. Costa Zaninotto; C. Donnelly; T. Storz; C. Lubeski; M. MacDougall; K. Kelly; A. Hendricson; K. Fraser; S. Korsten; P. Kremer; A. Cacace; I. Conti; P. Montenigro (Leiden, Netherlands)*

**LBA-1: Largest genotype-phenotype association study in Latin American cohorts highlights the role of ITPKB in PD risk**

*T.P. Leal; E. Waldo; F. Duarte-Zambrano; M. Inca-Martinez; J. Ramchandra; H.M. Chaparro-Solano; A.E. Anello; V. Borda; M.H. Gouveia; D. Teixeira-dos-Santos; P. Reyes-Pérez, E.M. Gatto; C. Perandones; M. Radrizzani; B.L. Santos-Lobato; G.L. Eufraseo; G.H. Letro; G. Arboled; O. Bernal-Pacheco; J. Orozco; B. Munoz; P. Chana-Cuevas; X.P. Corres; D. Aguillon; O. Buritica; G. Torrealba-Acosta G; M.V. Muller; C.M. Lopez-Razquin; P. Braga-Neto; R.M. Durón, M. Rodríguez-Violante; A.J. Hernández-Medrano; A. Cervantes-Arriaga; D. Martinez-Ramirez; A.F.S. Schuh, C.R.M. Rieder; M. Cornejo-Olivas; J. Rios-Pinto; A. Vinuela; V. Tumas; A.V. Pimentel; V. Borges; E.R. Barboso; C.L. Avila; P. Olguin; A. Colombo; J.C. Nunez; A. Medina-Rivera; A.E. Ruiz-Contreras; S. Alcauter; E. Dieguez; K. Nuytemans; Global Parkinson's Genetics Program (GP2); Latin American Research Consortium on the Genetics of Parkinson's Disease; I. Mata (Cleveland, OH, USA)*

Objective: We aim to identify genetic risk loci associated with Parkinson's disease susceptibility in Latin American populations by conducting the largest genome-wide association study (GWAS) of PD in this population.

Background: The Latin American Research Consortium on the Genetics of PD (LARGE-PD) is a multicenter collaboration aimed at understanding the genetic architecture of PD in this population using data from 15 countries across the Americas and the Caribbean.

Methods: We analyzed genotype data from LARGE-PD Phase 1 (n = 1,504) and Phase 2 (n = 4,400) using multiple GWAS approaches: SAIGE, which incorporates genetic relationship matrix in the model; ATT, which includes global ancestry on the model; TRACTOR, which splits allele dosages by ancestry to detect ancestry-specific risk loci; and admixture mapping. We also assessed linkage disequilibrium (LD) patterns and performed Meta-Regression of Multi-AncEstry Genetic Association (MR-MEGA), integrating data from both LARGE-PD phases and two South Asian GWAS (Andrews et al., 2023; Kishore et al., 2025).

Results: We identified PD-associated loci on chromosomes 1 and 4 (Figure 1). Our results replicated previous findings, including the well-established SNCA variant rs356182-A (OR = 1.517, $p = 1.62\times10^{-16}$). Notably, we identified a locus in ITPKB (rs117185933-A, OR = 1.75, $p = 3.8\times10^{-12}$), which had the highest CADD Phred score (17.92, top ~3% most deleterious) among all candidate variants, suggesting strong functional relevance. Functional annotation predicted that this variant may create a premature start codon in the 5' UTR of ITPKB. Although rs117185933-A is in high LD ($r^2 > 0.8$) with a variant previously reported by Kishore et al. (2025), our LD analysis and MR-MEGA results indicate that this signal is correlated with ancestry heterogeneity and likely represents an independent PD risk loci (Figure 2). This variant is more common in admixed American populations in gnomAD (MAF = 0.083) and SAS (MAF = 0.07), but nearly absent in non-Finnish Europeans (MAF = 0.0002).

Conclusion: We identified PD-associated variants in SNCA and ITPKB, the latter not previously reported in European-ancestry studies. The ITPKB variant may lead to a start codon gain in a gene with known protective effects against α-synuclein aggregation in in-vivo and in-vitro

models. These findings show the importance of including underrepresented populations in genetic research to uncover ancestry-specific risk loci and advance precision medicine for PD.

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**LBA-2: Interpretable deep learning framework for PSG-based classification of REM sleep behavior disorder and Parkinson's disease**

*Y.J. Jung; S. Kim; J. Jeong (Seoul, South Korea)*

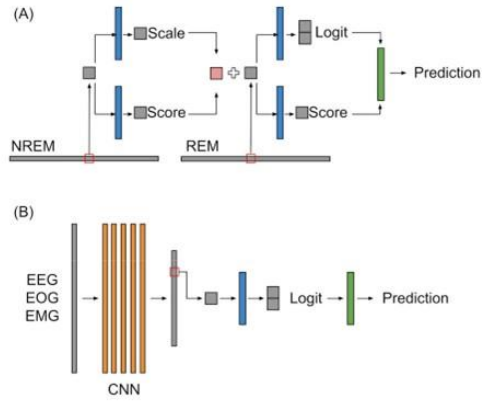
Objective: The objective of this study is to develop a robust and interpretable deep learning framework to classify REM sleep behavior disorder (RBD) and Parkinson's disease (PD) across multi-center polysomnography (PSG) datasets.

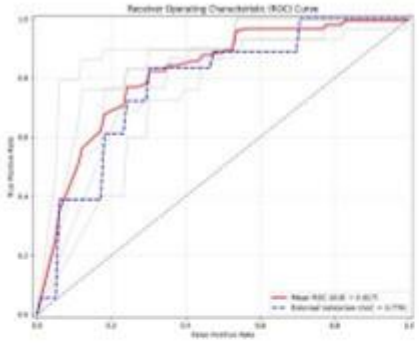
Background: Early identification of PD remains a critical frontier. While RBD is a well-established prodromal marker, conventional PSG-based diagnostic approaches are limited in generalizability and interpretability. Moreover, the predominant focus on REM sleep may obscure NREM sleep.

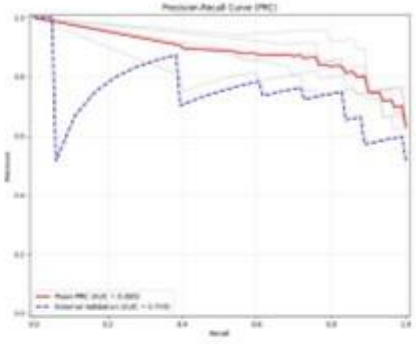
Methods: We analyzed PSG data from 233 individuals (PD with/without RBD, isolated RBD, controls) across four clinical centers. Our framework consisted of two parallel AI pipelines: an RBD classifier using chin EMG during REM, and a PD classifier leveraging multi-channel EEG, EOG, and EMG (Figure 1). We introduced subject-specific EMG normalization based on NREM segments to enhance inter-center robustness. Signals were segmented into 3-second mini-epochs, and attention-weighted diagnostic scores were computed. For PD classification, we further incorporated sleep stage information and latent space clustering.

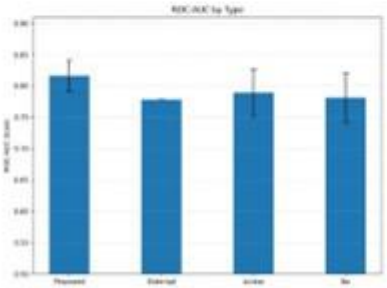
Results: Our framework achieved strong performance: AUC = 0.817 for RBD (Figure 2) and AUC = 0.792 for PD (Figure 3). Two key findings emerged: 1) NREM sleep was more informative than REM sleep for PD classification. Model performance showed minimal degradation when using only NREM (N2: −1.5%, N3: −2%), while REM alone showed the largest performance decrease (−10%) (Figure 4). 2) PD patients exhibited a markedly reduced sleep pattern diversity during N2, occupying only 31% of the pattern diversity seen in controls (Δentropy ≈ −1.7 bits) (Figure 5), indicating a collapse in neurophysiological flexibility. Additionally, our RBD classifier revealed adaptive amplitude normalization strategies by learning subject-specific baselines, outperforming traditional methods.

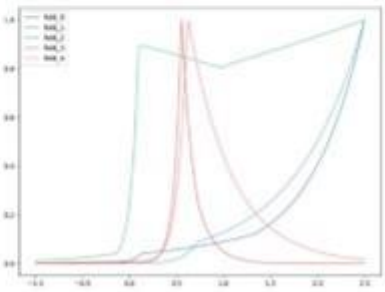
Conclusion: Our interpretable deep learning framework not only achieves robust cross-center classification of RBD and PD using standard PSG but also provides novel insights into the pathophysiology of neurodegeneration. The findings challenge prevailing REM-centric paradigms and suggest that reduced neural flexibility during sleep may be a core feature of early PD. By uniting strong diagnostic performance with interpretability, this work establishes a clinically scalable paradigm for AI-assisted neurological diagnosis.

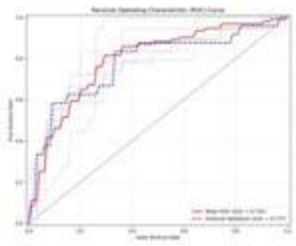


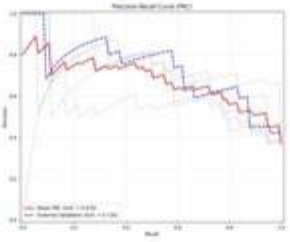


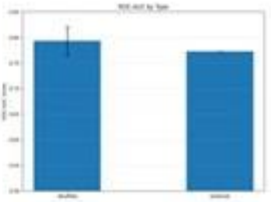


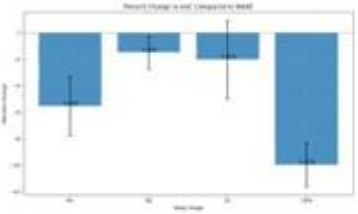


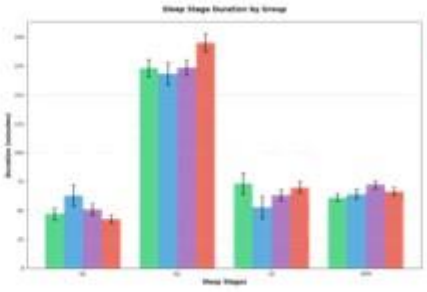


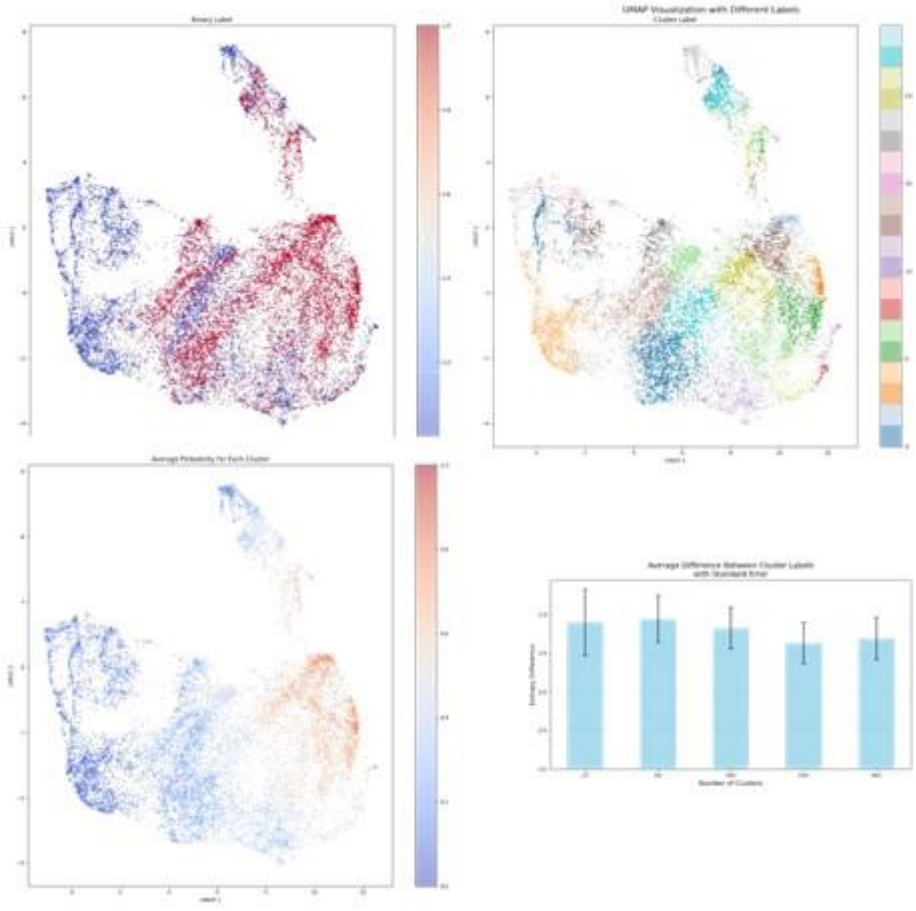












**LBA-3: Long-Term Efficacy and Safety of Omaveloxolone in Patients With Friedreich Ataxia: 4-Year Data From the Ongoing MOXIe Open-Label Extension**

*T. Zesiewicz; D.R. Lynch; M.B. Delatycki; J.C. Hoyle; S. Boesch; W. Nachbauer; P. Giunti; G. Wilmot; S.H. Subramony; K.D. Mathews; S. Perlman; R. Lawson; C. Shen; S. Farooq; S. Natarajan; R.M. Domingo-Horne; A. Arizpe; N. Folschweiller; M. Murai (Tampa, FL, USA)*

Objective: To evaluate the long-term efficacy, safety, and tolerability of omaveloxolone (omav) in patients with Friedreich ataxia (FA) treated for ≈4 years in the MOXIe open-label extension (OLE).

Background: Omav is approved for treatment of FA in patients aged ≥16 years. The OLE assessed long-term efficacy, safety, and tolerability of omav in eligible patients with FA following completion of MOXIe Part 1 or Part 2 (NCT02255435). In MOXIe Part 2, omav-treated patients experienced a benefit in neurological function (modified Friedreich Ataxia Rating Scale [mFARS] score) relative to placebo at 48 weeks. FA progression has been reported to be +1.8-2.0 mFARS points/year in natural history studies.

Methods: This analysis of the MOXIe OLE (data cutoff: February 27, 2025) reports data to ≈4 years, beginning from extension Day 1 (baseline) through Week 216. We report mean change in mFARS and FA Activities of Daily Living (FA-ADL) scores in patients who were treatment naive upon entry into the OLE (all patients from Part 1 and placebo-treated patients from Part 2; placebo-omav), those who received omav in Part 2 and continued treatment in the OLE (omav-omav), and the pooled population. Safety and tolerability were continually assessed.

Results: Overall, 149 patients were included in this analysis (43 omav-omav, 106 placebo-omav). Consistent with initiating treatment earlier, patients in the omav-omav group had lower baseline mean (SD) mFARS scores (41.2 [12.0] versus 43.3 [12.7]) and FA-ADL scores (12.0 [5.16] versus 12.7 [4.92]) than the placebo-omav group. Patients treated with omav demonstrated a mean (SD) change from baseline in mFARS scores of 4.40 (6.26) (+1.1 points/year) and FA-ADL scores of 2.79 (3.04) (+0.7 points/year) over 4 years, with comparable findings in the omav-omav and placebo-omav groups (Table). Continued omav treatment was associated with no worsening in two mFARS subdomains: bulbar function and upper limb coordination. Safety findings were consistent with previous reports.

Conclusion: Findings from the MOXIe OLE, the longest study of a disease-modifying therapy in patients with FA, showed slow disease progression with ≈4 years of omav treatment (+1.1 versus ≈2.0 mFARS points/year observed in natural history studies), with no significant disease progression in bulbar function and upper limb coordination, underscoring omav's potential to alter the course of FA.

**Table. Change From Baseline in mFARS at ≈4 Years[a,b]**

| Change from baseline, mean (SD) | Placebo-omav (N=106) | Omav-omav (N=43) | Overall omav (N=149) |
|---|---|---|---|
| **Total mFARS scores (range, 0-99)** | 4.36 (6.83) | 4.49 (4.97) | 4.40 (6.26) |
| **mFARS subscales** | | | |
| Bulbar function | **−0.17 (0.53)** | **−0.21 (0.52)** | **−0.18 (0.52)** |
| Upper limb coordination | **−0.58 (3.63)** | **−1.04 (2.93)** | **−0.73 (3.41)** |
| Lower limb coordination | 1.80 (3.20) | 1.85 (2.68) | 1.82 (3.03) |
| Upright stability | 3.31 (3.35) | 3.89 (2.72) | 3.50 (3.16) |

mFARS = modified Friedreich Ataxia Rating Scale; omav = omaveloxolone.
[a] This analysis includes those patients in the MOXIe open-label extension with the opportunity to reach Week 216 as of the data cut-off date of February 27, 2025.
[b] In a natural history cohort, mean (SD) change from baseline to Year 4 in mFARS score was +8.22 (8.49) (Patel M, et al. *Ann Clin Transl Neurol.* 2016;3[9]:684-694).

**LBA-4: N-acetyl-L-leucine: Findings from the Extension Phase of a Phase II Clinical Trial in Ataxia-Telangiectasia**

*M. Patterson; B. Zanrucha; J. Raymond; A. Hatcher; J. Kerthi; T. Fields; I. Billington; M. Strupp (Austin, TX, USA)*

Objective: Share learnings from Extension Phase of a Phase II clinical trial in ataxia-telangiectasia.

Background: N-acetyl-L-leucine (NALL) is a modified amino acid which enters enzyme-controlled pathways and corrects metabolic dysfunction, improves lysosomal and mitochondrial function, and restores membrane potential and cellular signaling. Clinical studies of NALL in Niemann-Pick disease type C (NPC), GM2 Gangliosidoses (GM2), and ataxia telangiectasia (A-T) consistently demonstrated that NALL significantly improves neurological signs and symptoms like ataxia.

IB1001-203 was a Phase II trial investigating NALL in patients ≥6 years with Ataxia Telangiectasia (A-T). Following the initial study, patients were given the option to continue treatment in the Extension Phase (EP), which we present here.

Methods: The primary endpoint was defined as the change from the Extension Phase baseline versus the end of the first year of treatment with NALL in the Extension Phase Treatment Period I on the Scale for the Assessment and Rating of Ataxia (SARA).

Exploratory endpoints included the change in SARA change during the Extension Phase Washout Period and the change from the end of the second year of treatment with NALL in the Extension Phase Treatment Period I versus the Extension Phase Baseline.

Results: 12 patients aged 6 to 36 years have completed Visit 9 of the Extension Phase. After 12 months of treatment, the mean change from baseline on the SARA -2.25 ± 3.16 points after receiving NALL (95% confidence interval [CI] -4.25 to-0.25; p=0.031).

The mean change in SARA for participants (n =11) during the Extension Phase Washout Period was 1.36 (SD=2.04) (95% confidence interval [CI] 0 to 2.73; p=0.25).

Following the EP Washout Period, 7 patients completed treatment with NALL for an additional 1 year. The mean change in SARA score compared to the start of the Extension Phase was -0.33.

Conclusion: In the IB1001-203 Extension Phase involving patients with A-T, treatment with NALL corresponded to a 340% reduction in annual disease progression after 1 year and 120% after 2 years compared to a natural history control cohort. Treatment with NALL prevented worsening and improved disease status, reflecting a neuroprotective and disease-modifying benefit.

Following positive results with NALL in NPC and GM2, a global Phase III study (IB1001-303) has been initiated.

**LBA-5: Blood extracellular vesicles-based alpha-synuclein biomarker for predicting synucleinopathy clinical symptoms, CSF alpha-synuclein seeding assay, and postmortem positivity.**

*E. Eitan; O. Volpert; S. Rau; A. Gekas (Natick, MA, USA)*

Objective: Synucleinopathies—including Parkinson's disease, multiple system atrophy (MSA), and Lewy body dementia—affect over 27 million individuals globally. The clinical presentation and prognosis vary based on the anatomical distribution and burden of alpha-synuclein pathology within the brain. Despite their prevalence and impact, these disorders remain challenging to diagnose and monitor, with no available blood-based tests for screening or disease progression tracking.

Background: Neuron-derived extracellular vesicles (NDEs) have emerged as a promising platform for blood-based detection of alpha-synuclein. Enriching for NDEs enables brain-specific measurement, circumventing the confounding effects of abundant peripheral alpha-synuclein. However, the development of a reliable, scalable assay for quantifying NDE-associated alpha-synuclein remains a significant challenge. This study makes substantial progress toward addressing this gap..

Methods: ExoSORT with GAP43 and NLGN antibodies was used for NDE enrichment. Mesoscale and Luminex alpha-synuclein assays were used for analysis, and the CD9 LuminEV assay was used for normalization. The aSyn assay qualification includes within-batch variability of 7% (10-individual, 3-repeats), between-batch variability of 13% (two pool plasma,17-batches), and linearity ($R=0.73$, $P<0.01$)

Results: Alpha-synuclein levels in neuron-derived extracellular vesicles (NDEs) were significantly elevated in patients with clinically diagnosed Parkinson's disease (PD; N=113) compared to healthy controls (N=193; $P < 0.0001$), yielding an AUC of 0.84, with 82% sensitivity and 83%

specificity. Elevated NDE alpha-synuclein levels were also observed in patients with Lewy body dementia (LBD; N=37; P < 0.001; AUC = 0.91), and levels were unaffected by GBA mutation status. In patients with multiple system atrophy (MSA; N=65), NDE alpha-synuclein was modestly elevated (P < 0.04; AUC = 0.67), while oligodendrocyte-derived EVs (ODEs) showed a stronger increase (P < 0.007; AUC = 0.74). In a cohort with postmortem-confirmed LBD pathology (N=27), NDE alpha-synuclein levels remained significantly elevated (P < 0.001; AUC = 0.92). Finally, in a PD cohort validated by CSF alpha-synuclein seeding assay (N=24), NDE alpha-synuclein showed a robust diagnostic performance (P < 0.001; AUC = 0.92), with 81% sensitivity and 95% specificity.

Conclusion: Neuron-derived extracellular vesicles are a promising platform for developing a robust blood-based biomarker for Synucleinopathies. The current work demonstrate the promise across multiple cohorts with post-hoc analysis. The next stage will be to test the method perfromace with an add-hoc trashold.

**LBA-6: In Situ Detection of α-Synuclein Seeding Activity in Frozen Brain Sections**

*H. Mao; Y. Kuang (Guangzhou, Guangdong, People's Republic of China)*

Objective: To develop and validate a novel method, the Quiescent Seed Amplification Assay (QSAA), for the in situ amplification and visualization of α-synuclein (αSyn) seeding activity directly within tissue sections, preserving spatial information. A further objective was to combine QSAA with immunofluorescence (IF-QSAA) to simultaneously investigate the relationship between seeding activity and antibody-detected pathological aggregates.

Background: The prion-like propagation of misfolded α-synuclein (αSyn) aggregates, driven by their "seeding" activity, is a central mechanism in the pathogenesis of synucleinopathies like Parkinson's disease (PD). Current methods to detect pathological αSyn are limited. Antibody-based approaches (e.g., targeting pS129-αSyn) provide a static view of aggregate load but do not measure functional seeding activity. Conversely, conventional seed amplification assays (SAAs), while highly sensitive, require tissue homogenization and agitation, which destroys the crucial spatial information about where the seeds originate in the brain. This highlights a critical need for a technique that can sensitively detect αSyn seeding activity with high spatial resolution.

Methods: We developed the αSyn Quiescent Seed Amplification Assay (QSAA) by optimizing buffer conditions to achieve robust, seed-dependent amplification without mechanical agitation. This was accomplished by using a mouse αSyn substrate, adding sulfate ions ($SO_4^{2-}$), and elevating the reaction temperature to 70°C. We applied QSAA to brain sections from a mouse model of synucleinopathy (intrastriatal injection of αSyn pre-formed fibrils) and to postmortem human brain tissue from patients with PD, progressive supranuclear palsy (PSP), and healthy controls. We further developed IF-QSAA to co-visualize QSAA-amplified products (via Thioflavin T) and antibody-labeled targets (via Alexa Fluor 647), such as pS129-αSyn, total αSyn, and neuronal markers.

Results: QSAA successfully enabled rapid and specific in situ amplification of αSyn seeds in both mouse and human PD brain tissue, while no signal was observed in PSP or healthy control brains. We generated the first brain-wide map of αSyn seeding activity in a mouse model, revealing that the distribution of seeding activity was more extensive than pS129-αSyn immunoreactivity, particularly within white matter tracts. The IF-QSAA technique revealed that while seeding activity often co-localized with antibody-detected aggregates, a significant portion of seeding occurred independently of pS129-positive aggregates. This suggests that αSyn seeding and phosphorylation at Ser129 can be distinct pathological events.

Conclusion: QSAA and its derivative, IF-QSAA, are powerful new tools for the sensitive and specific visualization of αSyn seeding activity in situ. These methods provide critical spatial context that is lost in traditional SAAs and offer functional information not captured by standard immunohistochemistry. Our findings demonstrate that mapping seeding activity provides complementary, and at times distinct, information to antibody-based assessments of pathology. These techniques hold significant promise for advancing our understanding of synucleinopathy pathogenesis and for evaluating novel therapeutic strategies targeting αSyn propagation.

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**LBA-7: Vatiquinone Prevents Ferroptosis in Preclinical Models of Friedreich's Ataxia**

*J.K. Trimmer; J.C. Latham; A. Minella; A. Krieger; A. Karcini; S. Chaudhary; Y.J. Kang; Y. Mao; M. Weetall; J.J. Cherry (Warren, NJ, USA)*

Objective: To assess the preclinical effects of vatiquinone, a novel and potent 15-lipoxygenase (15-LO) inhibitor, being evaluated as a treatment for Friedreich's ataxia (FRDA).

Background: Ferroptosis, a regulated form of cell death, results from iron-dependent accumulation of toxic lipid hydroperoxides. 15-LO is a critical enzyme in the pathway leading to peroxidation and ferroptosis. Under normal conditions, glutathione (GSH) peroxidase 4 (GPX4) detoxifies cells by neutralizing lipid hydroperoxides in a GSH-dependent reaction. Vatiquinone prevents ferroptosis by inhibiting 15-LO, thus sparing GSH. 15-LO plays a key role in FRDA. FRDA is caused by frataxin (FXN) deficiency; FXN is crucial for the synthesis of iron-sulfur cluster proteins. Without FXN, iron accumulation leads to increased oxidative stress, reduced GSH and GSH/glutathione disulfide (GSSG) ratios, accumulation of 15-LO lipid hydroperoxide products (hydroxyeicosatetraenoic acids [HETEs]) and increased ferroptosis.

Methods: A GSH-synthesis inhibitor (L-buthionine-sulfoximine) induced oxidative stress in fibroblasts from patients with mitochondrial diseases, including FRDA. The GPX4 inhibitor RSL3 induced ferroptosis in mice; high doses of RSL3 (150 mg/kg) elicited ferroptosis-dependent lethality, and lower doses (25 mg/kg) increased plasma HETEs and other markers of ferroptosis. Mice with a muscle-specific FXN knockout under the Mck promoter (cFAKO) had cardiac pathology. Vatiquinone was assessed for the ability to biochemically normalize fibroblasts and RSL3-dosed and cFAKO mice.

Results: Vatiquinone potently protected against oxidative stress-mediated cell death in fibroblasts (near maximal protection at 200 nM). In mice, vatiquinone dose-dependently reduced ferroptosis-induced lethality (80% survival at 300 mg/kg vs 40% with vehicle). At a lower dose, RSL3 was not lethal and increased 12-HETE 7-fold; vatiquinone (300 mg/kg) reduced 12-HETE by 65%. 12-HETE levels were 3.7-fold higher in cFAKO mice than wild-type (WT), and vatiquinone treatment (300 mg/kg) resulted in a 79% reduction. Cardiac GSH/GSSG ratios were reduced by 50% in cFAKO mice vs WT and were normalized by vatiquinone (300 mg/kg; 61% greater levels vs untreated).

Conclusion: These data confirm that vatiquinone has profound inhibitory effects on ferroptotic pathways in in vivo and in vitro preclinical models, protecting against underlying pathologies of FRDA, including accumulation of HETEs and GSH depletion.

**LBA-8: Results From the ELATE Trial: A Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of OnabotulinumtoxinA for the Treatment of Upper Limb Essential Tremor**

*A. Patel; K. Patterson; D. Kholsa; R. DeGryse; N.Y. Huang; R. Dimitrova; M.C. Munin; P. McAllister; C.A. Cooper; D.M. Simpson; S.H. Isaacson; R. Pahwa; R.L. Barbano; L. James (Overland Park, KS, USA)*

Objective: To evaluate the efficacy and safety of onabotulinumtoxinA (onabotA) compared with placebo (pbo) for the treatment of upper limb essential tremor (ET) in adults.

Background: ET is the most common movement disorder, characterized by postural/kinetic tremor that affects ~25 million individuals worldwide [1-3]. Traditional oral pharmacologic therapies offer limited efficacy and have tolerability concerns while secondary nonpharmacologic treatments are invasive and carry procedure-related risks [3-5]. Local administration of botulinum toxin represents a promising alternative treatment option for upper limb ET by locally diminishing oscillating muscle contractions and improving symptom management without the limitations of existing treatments.

Methods: ELATE (NCT05216250) was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adults with upper limb ET. Eligible participants received two treatments of onabotA or pbo unilaterally in the dominant limb at 12-week intervals. The primary efficacy endpoint was the change from baseline (CFB) in the Tremor Disability Scale-Revised (TREDS-R) score across 7 unilateral items (total score out of 28) at Week 18 (analyzed as

the average across Weeks 15, 18, and 21) [6-7]. Safety monitoring included common and treatment-emergent adverse events (TEAEs) for the duration of the study. Study methodology has been previously reported [8].

Results: In the intent-to-treat population, 182 participants were randomized 1:1 to receive pbo (n=87) or onabotA (n=95). Baseline demographics were similar between groups [Table 1]. The least squares mean CFB in TREDS-R total unilateral score at Week 18 [Figure 1] was -1.61 for pbo and -2.61 for onabotA (LSMD [SE] = -1.00 [0.45]; 95% CI [-1.90, -0.11]; P = 0.029). The pbo and onabotA TEAE profiles were comparable apart from muscular weakness (MW), which was more frequent in onabotA group (24.5%) vs pbo (2.5%); MW events were mostly mild/moderate and transient [Table 2]. None of the TEAEs suggested a distant spread of toxin.

Conclusion: OnabotA demonstrated statistically significant and clinically meaningful improvements in tremor-related disability in activities of daily living among participants with upper limb ET compared with pbo. The overall safety results are generally consistent with the established safety profile of onabotA.

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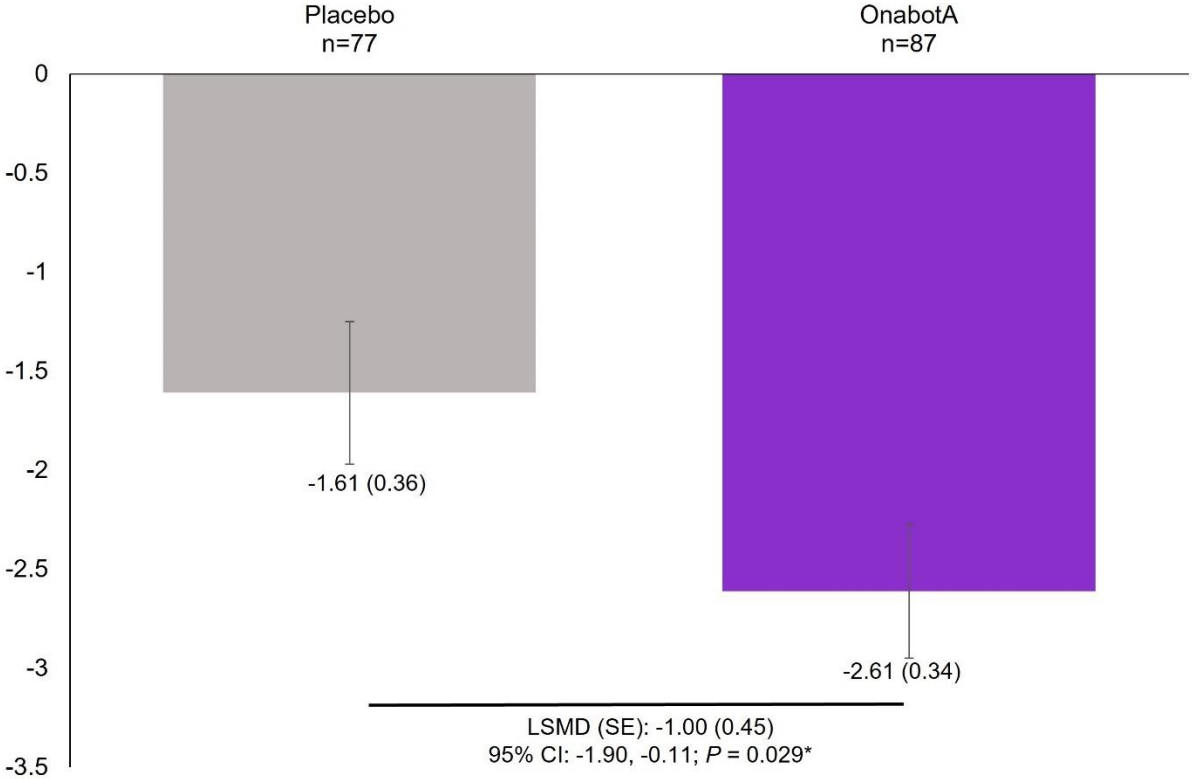
**Table 1**. Baseline Demographics and Disease Characteristics

| | Placebo (N=87) | OnabotA (N=95) | Total (N=182) |
|---|---|---|---|
| **Age (years)** | | | |
| *Mean (SD)* | 68.4 (8.10) | 68.5 (7.53) | 68.4 (7.79) |
| ≥70 years of age, n (%) | 43 (49.4) | 51 (53.7) | 94 (51.6) |
| **Male, n (%)** | 47 (54.0) | 55 (57.9) | 102 (56.0) |
| **BMI (kg/m$^2$), mean (SD)** | 30.1(7.63) | 29.7 (7.23) | 29.9 (7. 40) |
| **Age of onset (years), mean (SD)** | 51.8 (18.64) | 51.4 (18.50) | 51.6 (18.51) |
| **Time since onset (years), mean (SD)** | 18.4 (16.10) | 19.5 (17.53) | 19.0 (16.82) |
| **TREDS-R total unilateral score, mean (SD)** | 18.5 (2.69) | 18.5 (2.61) | 18.5 (2.64) |

BMI, body mass index; SD, standard deviation; TREDS-R, Tremor Disability Scale-Revised.

**Figure 1**. LS Mean Change From Baseline in Mean TREDS-R Total Unilateral Score at Week 18 (ITT Population). The change from baseline was calculated from the average TREDS-R total unilateral score across Weeks 15, 18, 21. Between group differences were calculated for onabotA minus placebo with *P*-value and 95% CI obtained from a mixed-effects model repeated measures (MMRM) across double-blind treatment period adjusting for treatment, weeks, site, and treatment by week interaction as fixed effects, with baseline as covariate, and subject and residual errors as random effects.

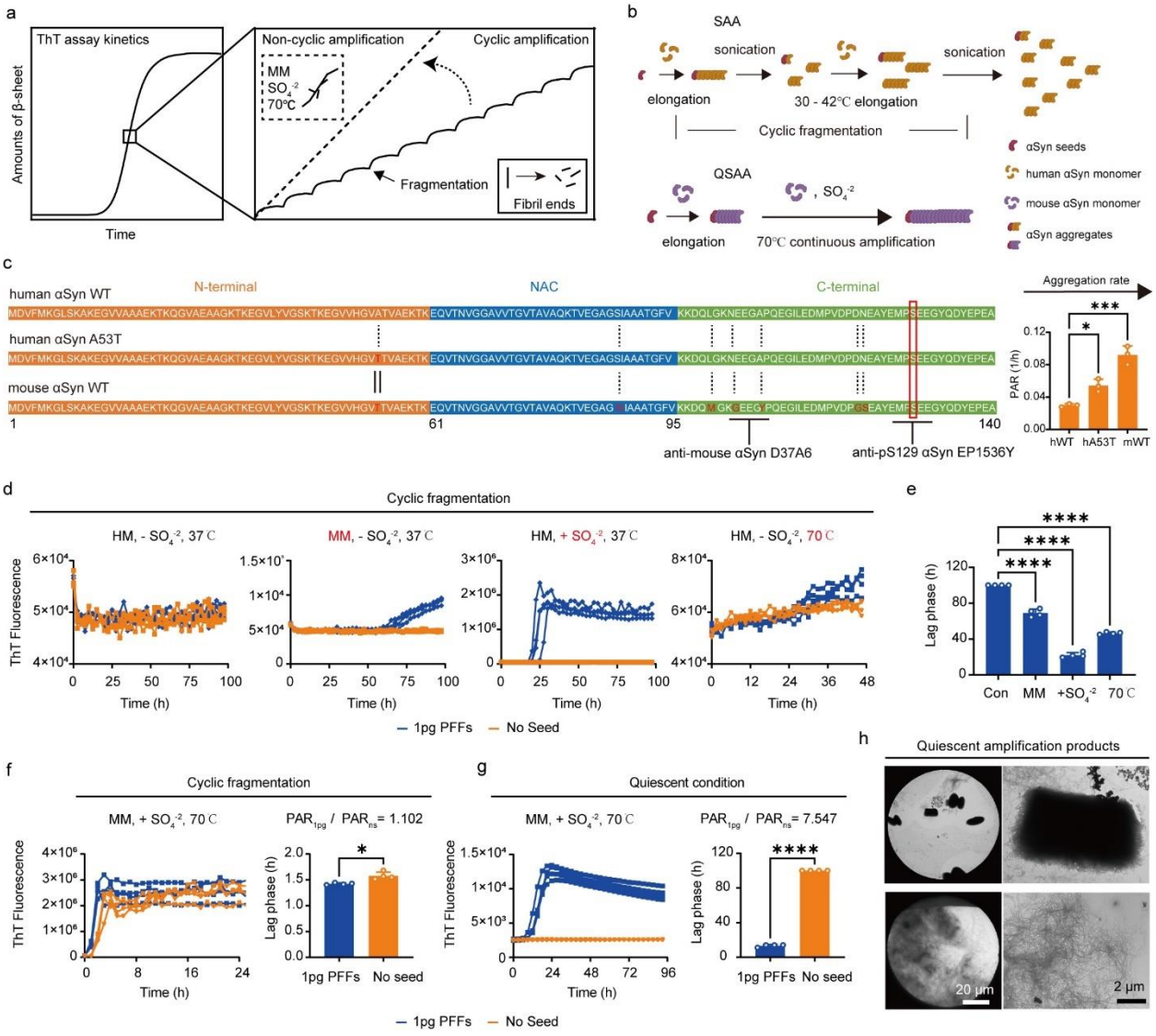



CI, confidence interval; ITT, intent-to-treat; LS, least squares; LSMD; least squares mean difference; SD, standard deviation; SE, standard error; TREDS-R, Tremor Disability Scale-Revised.
*$P < 0.05$.

**Table 2**. Summary of Events in the Safety Population During the Double-Blind Treatment Period*

| | Placebo (N=87) | OnabotA (N=94) | Total (N=181) |
|---|---|---|---|
| **Overall TEAEs** | 51 (58.6) | 60 (63.8) | 111 (61.3) |
| *Treatment-related TEAEs* | 3 (3.4) | 28 (29.8) | 31 (17.1) |
| *Serious TEAEs* | 7 (8.0) | 4 (4.3) | 11 (6.1) |
| **Death** | 1 (1.1)[a] | 1 (1.1)[b] | 2 (1.1) |
| **TEAEs occurring in ≥5% of onabotA population** | | | |
| *COVID-19* | 4 (4.6) | 6 (6.4) | 10 (5.5) |
| *Falls* | 4 (4.6) | 5 (5.3) | 9 (5.0) |
| *Muscular weakness* | 2 (2.3) | 23 (24.5) | 25 (13.8) |
| *Arthralgia* | 4 (4.6) | 5 (5.3) | 9 (5.0) |

TEAEs, treatment-emergent adverse events.
[a]Cause of death was reported as unknown/natural causes and considered to be unrelated to treatment by the investigator.
[b]Cause of death was reported as arteriosclerosis and considered to be unrelated to treatment by the investigator.
*Safety population includes all randomized subjects who had at least 1 study treatment intervention.


a
ThT assay kinetics
Non-cyclic amplification
Cyclic amplification
MM
$SO_4^{-2}$
70°C
Amounts of β-sheet
Time
Fragmentation
Fibril ends
b
SAA
sonication
elongation
30 - 42°C elongation
Cyclic fragmentation
αSyn seeds
human αSyn monomer
mouse αSyn monomer
αSyn aggregates
QSAA
elongation
70°C continuous amplification
c
human αSyn WT
N-terminal
NAC
C-terminal
human αSyn A53T
mouse αSyn WT
1
61
95
140
anti-mouse αSyn D37A6
anti-pS129 αSyn EP1536Y
Aggregation rate
PAR (1/h)
hWT
hA53T
mWT
d
Cyclic fragmentation
HM, - $SO_4^{-2}$, 37 C
MM, - $SO_4^{-2}$, 37 C
HM, + $SO_4^{-2}$, 37 C
HM, - $SO_4^{-2}$, 70 C
ThT Fluorescence
Time (h)
1pg PFFs
No Seed
e
Lag phase (h)
Con
MM
+$SO_4^{-2}$
70 C
f
Cyclic fragmentation
MM, + $SO_4^{-2}$, 70 C
$PAR_{1pg}$ / $PAR_{ns}$= 1.102
1pg PFFs
No seed
g
Quiescent condition
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h
Quiescent amplification products
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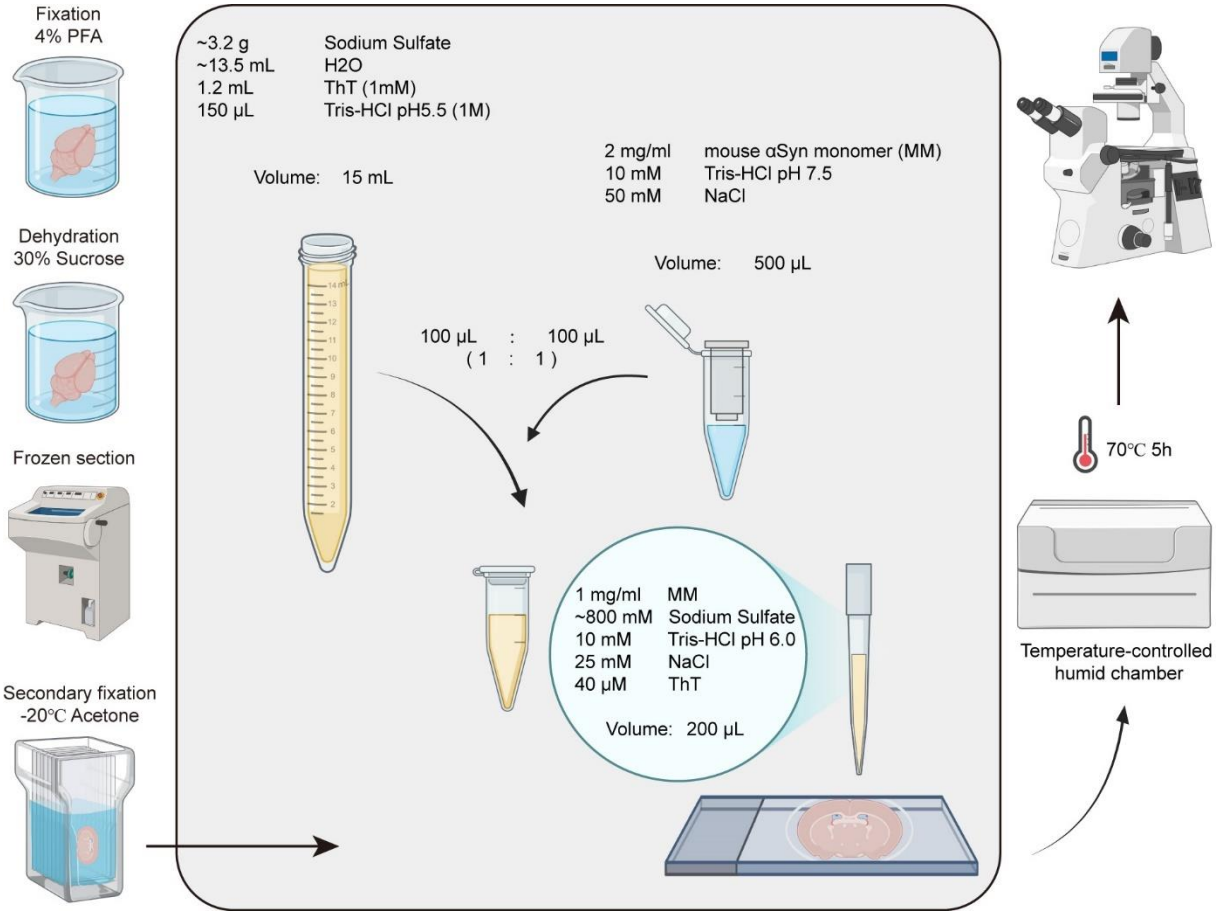
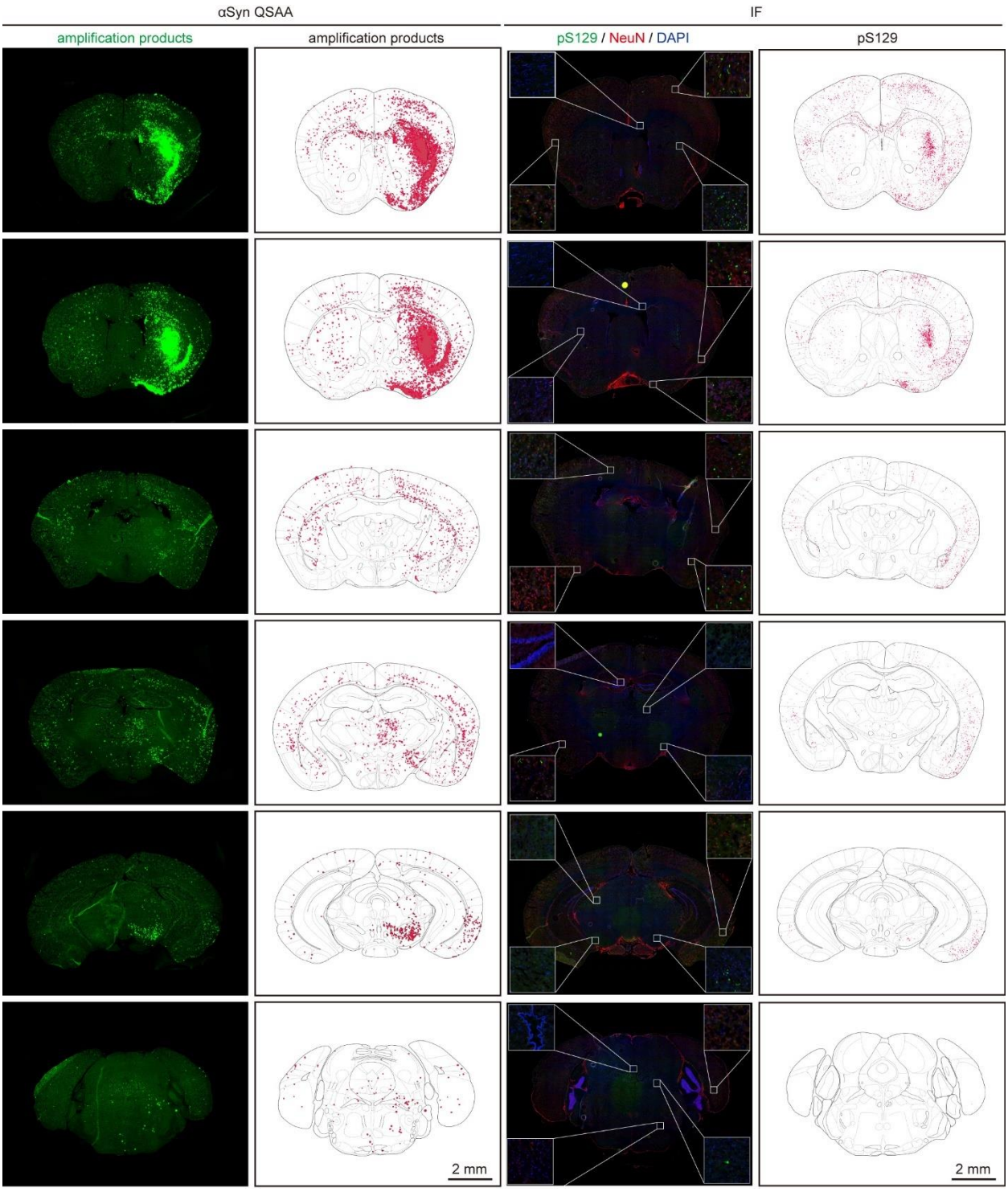
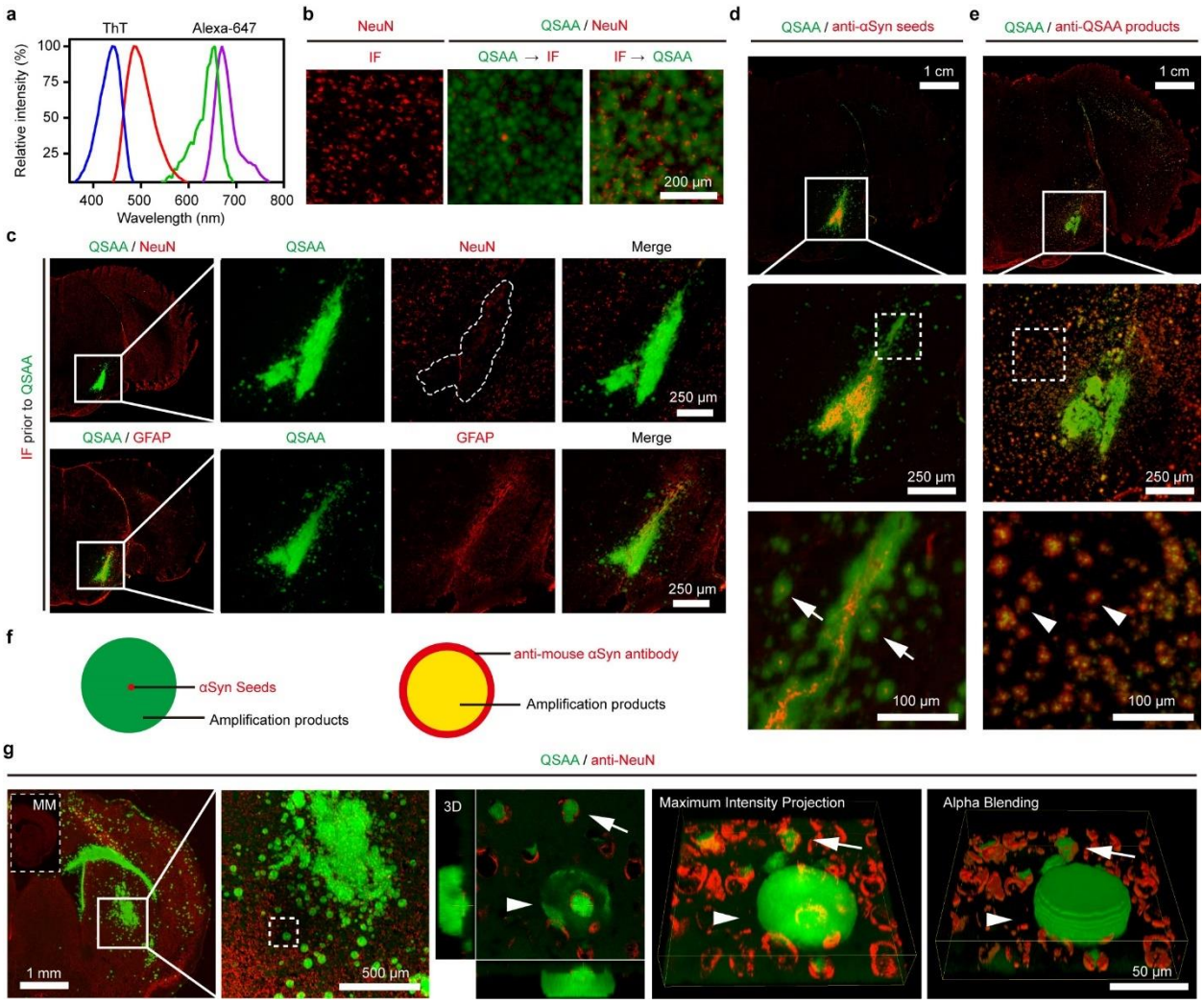
2 μm


Fixation
4% PFA
Dehydration
30% Sucrose
Frozen section
Secondary fixation
-20°C Acetone
~3.2 g Sodium Sulfate
~13.5 mL H2O
1.2 mL ThT (1mM)
150 µL Tris-HCl pH5.5 (1M)
Volume: 15 mL
2 mg/ml mouse αSyn monomer (MM)
10 mM Tris-HCl pH 7.5
50 mM NaCl
Volume: 500 µL
100 µL : 100 µL
( 1 : 1 )
1 mg/ml MM
~800 mM Sodium Sulfate
10 mM Tris-HCl pH 6.0
25 mM NaCl
40 µM ThT
Volume: 200 µL
70°C 5h
Temperature-controlled
humid chamber


αSyn QSAA
IF
amplification products
amplification products
pS129 / NeuN / DAPI
pS129
2 mm
2 mm




**LBA-9: Mechanism of Action, Preclinical Efficacy, and Safety Evaluation of SAN711/ACP-711, a Novel $GABA_A$ Subunit $\alpha_3$ Selective Modulator**

*D.V. Amrutkar; K. Sandager-Nielsen; T. Dyhring; T. Jacobsen; J. Larsen; P. Muglia; R. Hofbauer; S. Pathak; H. Lin (Glostrup, Hovedstaden, Denmark)*

Objective: Evaluate the pharmacology, efficacy, and adverse effects (AEs) of SAN711, also known as ACP-711, a $GABA_A$ receptor (R) subunit $\alpha_3$ selective modulator in vitro and in preclinical animal models of essential tremor (ET).

Background: ET is one of the most common neurological diseases, with the exact etiology currently unknown. Dysfunctional GABA signaling may play a role, however many GABAergic medications have significant AEs when treating ET. SAN711/ACP-711 is a novel $GABA_AR$ subunit $\alpha_3$ selective positive allosteric modulator (PAM) designed to have an improved AE profile compared to other GABAergic drugs.

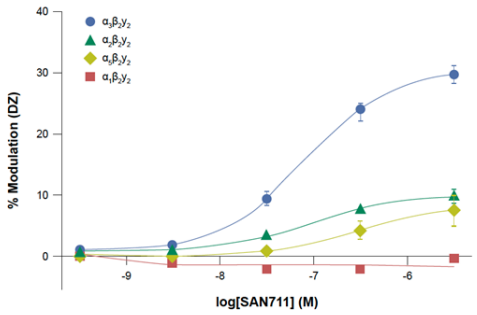
Methods: The efficiency of SAN711 to modulate $GABA_AR$ subtype activity was explored in *X. laevis* oocytes expressing human $GABA_ARs$, with α subunit subtypes 1, 2, 3, or 5. In vivo binding of SAN711 to mouse forebrain $GABA_ARs$ was evaluated by following SAN711 doses with injections of $^3$H-flumazenil, which binds selectively and with high affinity to $GABA_ARs$.

Antitremor properties of SAN711 were assessed in rats using a harmaline model of ET. Potential AEs associated with $GABA_AR$ modulation, such as sedation and motor coordination, were evaluated in rat models using non-selective $GABA_A$ PAM diazepam as a comparator. Sedative effects were tested by monitoring exploratory locomotor activity. Motor coordination was evaluated using a rotating accelerating rod (RotaRod) device.

Results: In *X. laevis* oocytes, SAN711 was shown to be a potent positive allosteric modulator of $GABA_AR$ with $EC_{50}$s in the 85-280 nM range, and an efficiency selectivity order of $\alpha_3\beta_2\gamma_2 > \alpha_2\beta_2\gamma_2 = \alpha_5\beta_2\gamma_2 >> \alpha_1\beta_2\gamma_2$ (Fig 1). SAN711 inhibited in vivo binding of $^3$H-flumazenil in the mouse forebrain; the estimated $ED_{50}$ was 0.7 mg/kg corresponding to a plasma concentration of 0.32 µM, determined based on percent inhibition of binding (Table 1).

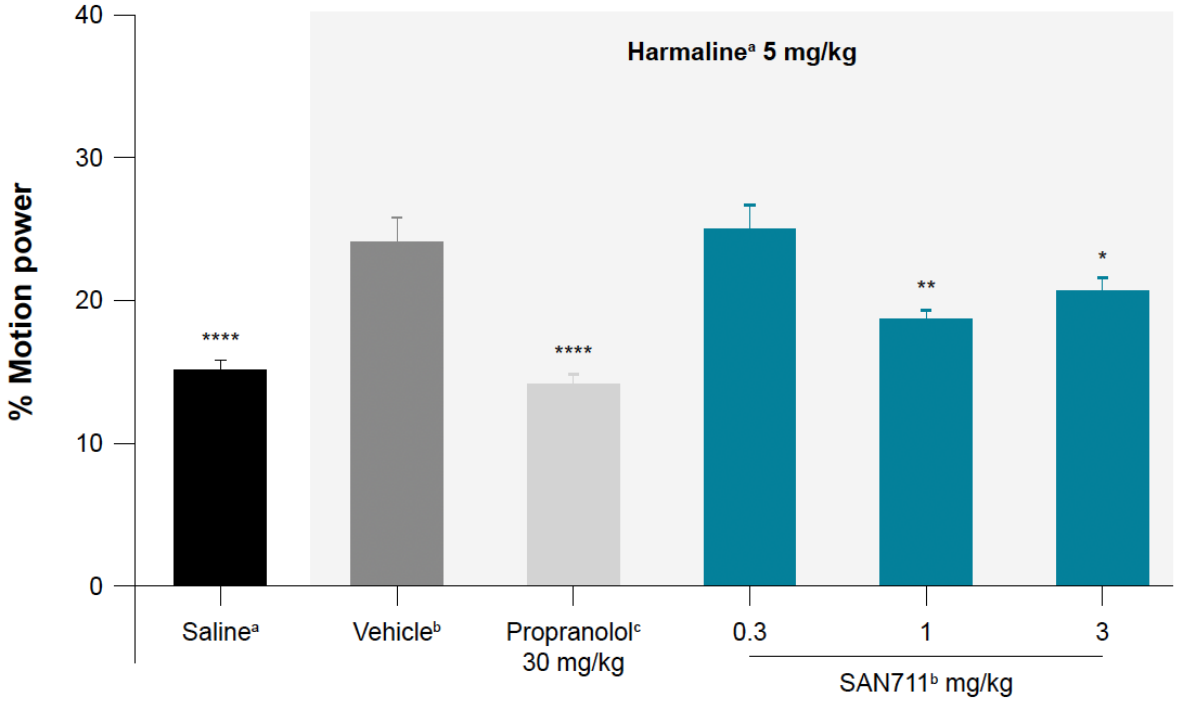
SAN711 dose-dependently decreased harmaline-induced tremors in rats evident by a significant reduction in motion power percentage, with a minimal effective dose of 1 mg/kg (Fig 2). Effects on activity and motor coordination of SAN711 in doses up to 30 mg/kg were not significantly different from vehicle (Fig 3). In contrast, the active control diazepam led to significant sedation and motor impairment.

Conclusion: SAN711 is a novel selective modulator of α3-containing GABAARs. In rodent models, SAN711 has shown efficacy in treating harmaline-induced tremors with no detectable AEs.



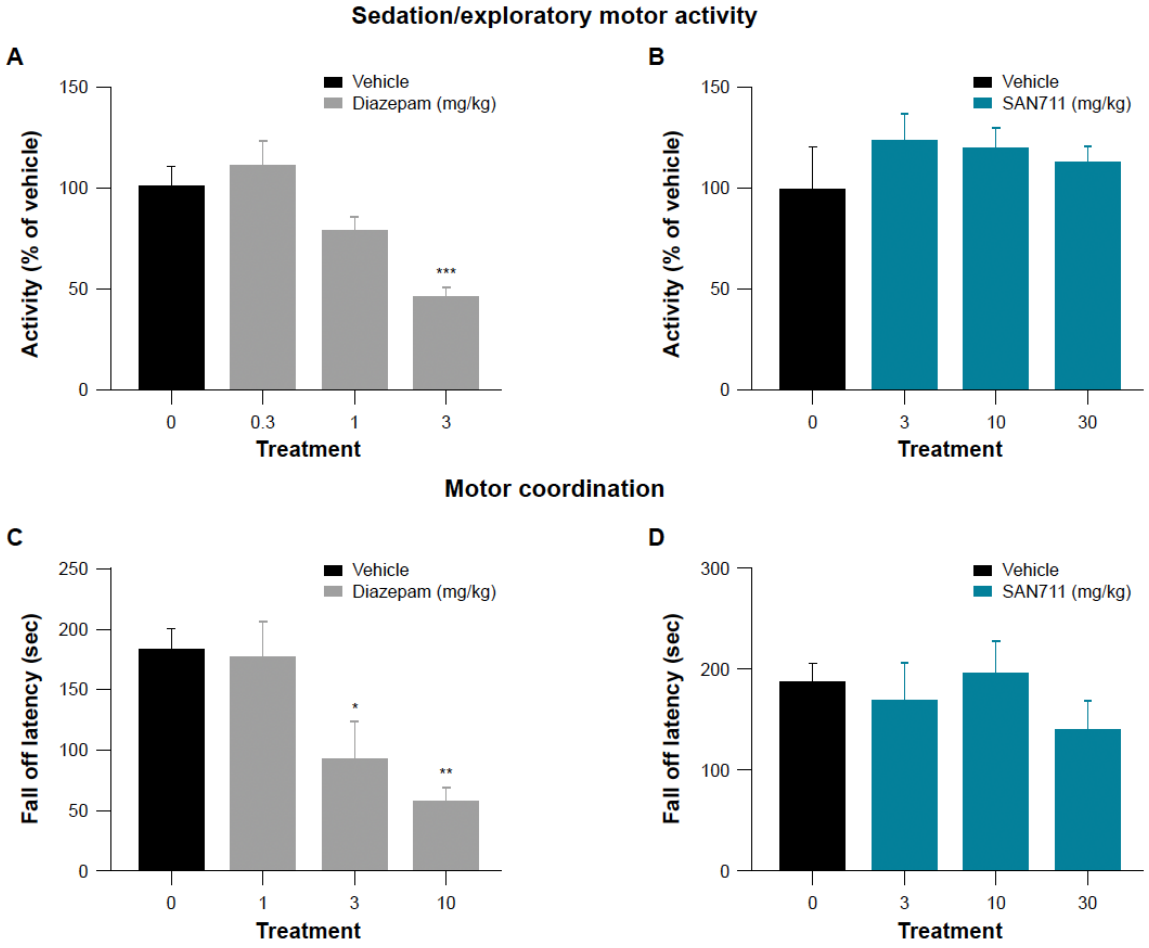

| | $\alpha_1\beta_2\gamma_2$ | $\alpha_2\beta_2\gamma_2$ | $\alpha_3\beta_2\gamma_2$ | $\alpha_5\beta_2\gamma_2$ |
|---|---|---|---|---|
| $E_{max}$(%) | -1.4 | 10 | 31 | 8.5 |
| $EC_{50}$(nM) | Undetermined | 90 | 85 | 280 |
| Number of oocytes | 8 | 3 | 14 | 6 |

**Figure 2.** Changes in Harmaline-Induced Tremors in Response to SAN711, Propranolol, or Vehicle in Rats.




[a]Values are mean ± SE. Motion power percentage is defined as the ratio of energy spent on tremor-like behavior divided by overall motion. A higher motion power percentage indicates worse tremors, with propranolol used as an active control for tremor reduction.
[a]Subcutaneous injection. [b]Oral administration. [c]Intraperitoneal injection.
SE, standard error.
* $P<0.05$; ** $P<0.01$; **** $P<0.0001$ vs vehicle.

**Figure 3.** Changes in Harmaline-Induced Tremors in Response to SAN711, Propranolol, or Vehicle in Rats.




Values are mean ± SE. All substances administered orally. A decrease in exploratory motor activity relative to vehicle indicates sedative effects. A reduced time for rats to fall off the RotaRod (fall off latency) indicates reduced motor coordination.
SE, standard error.
* $P<0.05$; ** $P<0.01$; *** $P<0.001$ vs vehicle.

**Table 1.** Plasma Concentration and Percent Inhibition of Binding of SAN711 to Mouse Forebrain GABAA Receptors.

| Dose (mg/kg)[a] | Inhibition of binding (%)[b] | Plasma conc . (µM)[c] |
|---|---|---|
| 0.1 | 13 | 0.035 |
| 1 | 57 | 0.5 |
| 10 | 97 | 8.0 |

[a]Oral administration.
[b]Percent inhibition after 2 h oral administration of SAN711 followed by tail vein injection of 2.0 µCi of $^{3}$H-flumazenil 10 min before sacrifice and analysis of forebrain tissue.
[c]Determined using LC-MS/MS of plasma samples.
Conc, concentration; LC-MS/MS, liquid chromatography-tandem mass spectrometry.

**LBA-10: A Multimodal Strategy Integrating Skin α-Synuclein and 4R-Tau SAAs with Circulating NfL to Support the Clinical Diagnosis of Parkinsonian Syndromes**

*I. Martinez-Valbuena; M. Abarghouei; D. Olszewska; M. Sousa; D. Di Luca; N.G. Reyes; S. Fereshtehnejad; C. Anastassiadis; J. Ta; J. Li; R. Cheung; J. Sasitharan; P. Bhakta; S.H. Fox; M.C. Tartaglia; G.G. Kovacs; A.E. Lang (Toronto, ON, Canada)*

Objective: To evaluate a multimodal, minimally invasive biomarker strategy combining α-synuclein (αSyn) and 4-repeat tau (4R-tau) seed amplification assays (SAAs) from skin biopsies with serum neurofilament light chain (NfL) to improve the diagnosis and stratification of parkinsonian syndromes.

Background: Diagnosing parkinsonian syndromes in early stages remains challenging due to overlapping clinical features and mixed pathologies. While αSyn-SAA and NfL have diagnostic value, their isolated use lacks specificity across disorders. A combined approach may enhance diagnostic precision and capture relevant co-pathologies.

Methods: We prospectively studied 169 participants (PD=41, MSA=29, PSP=79, controls=20) using a standardized 3-mm cervical skin biopsy and blood draw. αSyn- and 4R-tau SAAs were conducted on skin homogenates using commercial reagents. Serum NfL was quantified using an ultrasensitive immunoassay. Clinical diagnoses served as reference. ROC analyses determined optimal NfL thresholds to differentiate MSA from PD. Postmortem validation was available in 9 cases.

Results: αSyn-SAA distinguished synucleinopathies (PD and MSA) from PSP and controls with 87% sensitivity and 76% specificity. 4R-tau SAA identified PSP with 87% sensitivity and 93% specificity. NfL differentiated MSA from PD with an AUC of 0.94, a 28.8 pg/mL cutoff, 100% sensitivity, and 93% specificity. In all 9 autopsy-confirmed cases, pre-mortem biomarker results matched the definitive neuropathologic diagnosis. Notably, 22% of PSP cases were αSyn-SAA positive, indicating peripheral co-pathology associated with shorter disease duration.

Conclusion: This is the first study to demonstrate that misfolded αSyn and 4R-tau aggregates can be concurrently detected in vivo from a single skin biopsy. Combined with serum NfL, this multimodal strategy offers a biologically anchored, scalable tool to improve diagnostic accuracy and patient stratification in parkinsonian syndromes. Additionally, the detection of αSyn co-pathology in a subset of PSP patients—associated with shorter disease duration—suggests it may have clinical relevance, supporting the need to account for co-pathological burden in both diagnosis and therapeutic planning.

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**LBA-11: Protein signatures in Parkinson's disease and atypical Parkinsonisms**

*R. Real; R. Fumi; D. Vaughan; Y. Kordovska; O. Swann; A. Heslegrave; H. Zetterberg; H. Morris (London, United Kingdom)*

Objective: To analyse the blood proteome of a large cohort of clinically or pathologically defined PD, MSA, PSP, CBD, CBS and APS, with the aim of identifying disease-specific protein signatures.

Background: Parkinson’s disease is the most common neurodegenerative movement disorder, but the differential diagnosis can be difficult to establish. In particular, early stages of parkinsonian variants of MSA and PSP can present with similar symptoms. Routine investigations such as MRI and DaTscan lack specificity for PD. Alpha-synuclein seed amplification assays can help in establishing a diagnosis [1], but are invasive and not widely available. Therefore, there is a need to identify blood-based biomarkers that help distinguish between these disorders.

Methods: Baseline serum from 1466 participants was analysed with the NULISA multiplex immunoassay (CNS disease panel 120 v2)[2]. We performed linear regression to explore differentially abundant proteins between disease groups and controls. We then performed feature selection using Lasso regression to identify the proteins that most accurately differentiated between PD and other types of Parkinsonism. A sub-analysis was performed in the 40 cases with a pathologically defined diagnosis.

Results: After quality control, biomarker data from 1426 individuals were available for analysis (168 healthy controls, 847 PD, 185 PSP, 144 MSA, 45 CBS, 5 CBD, 32 APS). Comparing protein abundance in each disease group relative to controls revealed many statistically significantly targets that were shared across disease groups (n=43), while 58 targets were unique to PD, four targets were only significantly different in MSA and one target was specific to PSP. Of the targets unique to PD, we identified through feature selection a set of 31 proteins that could differentiate PD from non-PD Parkinsonism with an AUC of 0.906. When analysing the 40 cases with a pathologically confirmed diagnosis, a set of 9 unique proteins were significantly abundant in the 4R-Tau group, which could differentiate 4R-tauopathies from other proteinopathies (AD and alpha-synucleinopathy) with an AUC of 0.856.

Conclusion: The identification of blood proteins specific to PD and other Parkinsonisms suggests distinct protein signatures that could potentially be used as an early and minimally invasive diagnostic biomarker.

References:

1. Gomes BF et al. α-Synuclein seed amplification assay as a diagnostic tool for parkinsonian disorders. Parkinsonism Relat Disord 117, 105807 (2023).
2. Feng W et al. NULISA: a proteomic liquid biopsy platform with attomolar sensitivity and high multiplexing. Nat Commun 14, 7238 (2023).

**LBA-12: Safety, tolerability, pharmacokinetics and pharmacodynamics of VTX3232, a CNS-penetrant NRLP3 inhibitor, in participants with early-stage Parkinson's disease**

*R. Gregg; C. Christianson; K. Liu; T. Nguyen; R. Jucius; K. Ogilvie; B. Crean; J. Callahan; J. Nuss; M. Pomper; D. Russell; M. Forman (San Diego, CA, USA)*

Objective: The key objectives of the Phase 2a trial were to evaluate the safety, pharmacokinetics (PK), and pharmacodynamic activity of VTX3232 in participants with early-stage Parkinson's disease (PD).

Background: Neuroinflammation mediated by the NLRP3 inflammasome is increasingly recognized as playing a critical role in PD pathogenesis. NLRP3 is activated by pathologic α-synuclein, resulting in caspase 1-mediated release of IL-1β and IL-18, and an inflammatory form of cell death termed pyroptosis. VTX3232 is a potent oral inhibitor of NLRP3. Phase 1 studies in healthy adults demonstrated therapeutic concentrations in plasma and CSF at doses ≥12 mg and reduced NLRP3-mediated biomarkers.

Methods: Single-center, open-label Phase 2a study evaluated a 40 mg oral daily dose of VTX3232 in ten participants with early-stage PD over a 28-day treatment period (NCT06556173). Safety was assessed as the primary endpoint. VTX3232 concentrations and effects on NLRP3-related biomarkers (IL-1β, IL-18, IL-6, CRP) were evaluated in plasma and CSF. Exploratory endpoints included an assessment of PD symptoms via the MDS-UPDRS.

Results: VTX3232 was well-tolerated over 28 days with no drug-related treatment-emergent adverse events (AEs). All AEs were mild or moderate in severity. At steady state, mean VTX3232 concentration at 24 hours post-dose was 107.2 ng/mL in plasma and 30.4 ng/mL in CSF, >3-fold above the IC90 (~9 ng/mL) for NLRP3 inhibition. On day 28, IL-1β and IL-18 were reduced by 14-52% in plasma and CSF. Biomarkers downstream of IL-1β/IL-18 were reduced by 29-70% in plasma and CSF including IL-6, CRP and serum amyloid A. The largest decreases were observed in those individuals with elevated baseline values. Lastly, in this open label trial, VTX3232 was associated with improvement [mean] on the MDS-UPDRS in both motor (Part II, -2.7, p=0.0471; Part III, -5.2, p=0.0054) and non-motor (Part I, -2.4, p=0.0118) symptoms of PD.

Conclusion: Once daily administration of VTX3232 was well tolerated for 28 days in participants with PD. Drug exposure in CSF and plasma robustly inhibits NLRP3, exceeding the IC90 by >3-fold at trough. This positive Phase 2a study is a key milestone in advancing the development of

VTX3232 and NLRP3 inhibition as a potential disease-modifying therapy for PD and other neurodegenerative disorders.

References: Phase 2a Study of VTX3232 in Parkinson's Disease. ClinicalTrials.gov identifier: NCT06556173. Updated June 8, 2025. https://clinicaltrials.gov/study/NCT06556173.

**LBA-13: Phase 1/2a clinical trial of hESC-derived dopaminergic progenitors in Parkinson's disease**

H. Na; C.W. Park; K.W. Chang; M. Kim; D.H. Kim; S. Park. C.Y. Park; M.S. Kim; I. Jung; J.W. Chang; D.W. Kim; P.H. Lee (Seoul, South Korea)

Objective: To evaluate the safety and exploratory efficacy of intraputaminal engraftment of human embryonic stem cell (hESC)-derived dopaminergic progenitors (A9-DPCs) in patients with Parkinson's disease (PD).

Background: PD has long been considered an appropriate candidate for cell replacement therapy, considering its well-defined pathological hallmark selective loss of dopaminergic (DA) neurons in the substantia nigra pars compacta. Despite promising initial results of fetal tissue transplantation, its application has been limited by the inconsistent results in subsequent randomized trials, restricted tissue availability, and quality issues. Recent studies suggest that hESCs may provide a scalable source for generating DA progenitors with functional properties suitable for therapeutic application in PD.

Methods: We conducted a single-center, open-label, dose-escalation Phase 1/2a trial to evaluate the safety and exploratory efficacy of A9-DPC, an allogenic hESC-derived DA progenitor product. Twelve patients with moderate-to-severe PD were enrolled and assigned, using a 3+3 ruled-based method, to receive bilateral transplantation into the putamen of either a low-dose (3.15 million cells, n=6) or a high-dose (6.3 million cells, n=6). All patients received immunosuppressive therapy for 12 months. The primary endpoint was safety and tolerability. Exploratory efficacy endpoints included changes in the MDS-UPDRS score, Hoehn and Yahr (H&Y) stage, and 18F-FP-CIT PET imaging at 12 months.

Results: After cell transplantation, no dose-limiting toxicities or graft-related adverse events were observed in either group. At 12 months, compared with baseline, off-medication MDS-UPDRS Part III scores (−12.7 ± 8.2 in low-dose; −15.5 ± 3.6 in high-dose) and H&Y stage (−1.0 ± 0.6 in low-dose; −1.7 ± 0.5 in high-dose) improved. Motor function improved more in the high-dose group, consistent with a dose-dependent treatment effect. These clinical improvements were accompanied by increased 18F-FP-CIT uptake at the graft sites, supporting graft survival and functional DA activity.

Conclusion: Bilateral transplantation of A9-DPC into the putamen was safe and demonstrated clinical benefit over 12 months, providing preliminary evidence that this approach may offer a promising therapeutic strategy for improving parkinsonian motor symptoms in patients with PD (ClinicalTrials.gov number, NCT05887466).

References:

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**LBA-14: First-in-Human Study of Autologous iPSC-Derived Midbrain Dopaminergic Progenitors (UX-DA001) in Parkinson's Disease**

*L. Jun; C. Yuejun; L. Dianyou; T. Yuyan; L. Ningdi; Z. Liche; F. Haiyan; Y. Shanzheng. G. Juanhong; W. Junfeng (Shanghai, People's Republic of China)*

Objective: To evaluate the safety and efficacy of UX-DA001 in preclinical models and patients with Parkinson's disease (PD).

Background: PD is characterized by the loss of dopaminergic neurons (DA) in the substantia nigra. Cell therapies to replace lost dopaminergic neurons have hold promise for PD treatment. UX-DA001 is an autologous human iPSC-derived midbrain dopaminergic progenitors (mDAPs) product. We have demonstrated robust efficacy and safety of UX-DA001 in preclinical data supporting its IND approvals (China NMPA/U.S. FDA), and obtained exciting initial clinical data from an ongoing phase 1 trial (NCT06778265)

Methods: Preclinical studies included efficacy study in 6-OHDA-lesioned SCID mice and GLP toxicology/tumorigenicity study in NOG mice. The Phase 1 open-label dose-escalation trial enrolled moderate-advanced PD patients (50-75 years). Participants will receive bilateral injections into the putamen at either of the two dose levels: low-dose ($0.9 \times 10^6$ cells/hemisphere) and high-dose ($1.8 \times 10^6$ cells/hemisphere). Safety was monitored by an independent committee. No immunosuppression will be used in this trial.

Results: In preclinical studies, we observed reproducible high yields of in vivo mDA neurons across batches in a 6-OHDA-lesioned SCID animal disease model 6 months post-grafting. Over 50% of grafted cells were DA neurons, as verified by co-expression of specific cell markers TH and EN1. Functional recovery was confirmed by complete behavioral recovery and dopamine level restoration. GLP safety studies up to 6 months revealed no adverse effects. No tumor formation or abnormal proliferation was observed in tumorigenicity assessment up to 52 weeks.

In the first patient with 3-month follow-up, MDS-UPDRS Part III scores improved by 47.7% (21 points) in the OFF stage, and by 42.1% (8 points) in the ON state. Daily OFF-time reduced by 5.33 hours. Improvements were also observed in non-motor symptoms (e.g. sleep, anxiety, urinary) and PDQ-39 scores. $^{18}$F-FP-CIT PET confirmed graft survival. No drug-related AEs occurred; surgery-related AEs (headache, leukocytosis, dyskinesia) were mild and transient.

Conclusion: UX-DA001 demonstrates promising safety and efficacy in preclinical and initial clinical data, supporting its potential as a personalized cell therapy product for PD

**LBA-15: Real-World Safety and Effectiveness of Foslevodopa/Foscarbidopa in Parkinson's Disease: ROSSINI Study 6-Month Interim Results**

*W. Jost; F. Bergquist; A. Evans; S. Hassin-Baer; R. Hauser; T. Henriksen; I. Malaty; T. Mestre; P. Mir; R. Rodriguez; P. Schwingenschuh; M. Simu; L. Bergmann; R. Gupta; P. Kukreja; M. O'Meara; J.C. Parra; M. Shah; J. Aldred (Wolfach, Germany)*

Objective: Present first-ever multi-country real-world data from an ongoing 3-year observational study evaluating effectiveness and safety/tolerability of foslevodopa/foscarbidopa (LDp/CDp) in routine clinical practice

Background: LDp/CDp is delivered as a non-surgical continuous subcutaneous infusion over 24 hours (h) for people with advanced Parkinson's disease (PwP) and motor fluctuations uncontrolled on oral medications. Real-world data from routine clinical practice is limited.

Methods: ROSSINI (NCT06107426) is an ongoing 3-year multi-country, prospective, observational, two-cohort, open-label study of adults with advanced idiopathic PD. PwP naive to LDp/CDp (cohort A) or transitioning from LDp/CDp open-label extension studies (NCT04379050/NCT04750226, cohort B [not reported here]) receive LDp/CDp in routine clinical practice according to the locally approved label. The primary endpoint is change from baseline to 36 months(M) in OFF time (h, modified MDS-UPDRS IV item 4.3). Key secondary endpoints are listed in Table 2. Safety is assessed by adverse events (AEs). Here we present planned interim results for 100 cohort A participants with 6M of follow-up (cut-off 24 April 2025). Mixed-effects models for repeated measurements were used for continuous outcomes and generalized linear mixed-effects models for categorical outcomes, both adjusted for country.

Results: Analyses included 105 PwP in cohort A, with a mean (SD) age of 68.5 (9.5) years, PD duration of 12.1 (5.3) years, and mean (SE) 5.2 (0.5) h OFF time at baseline [Table 1]. The mean daily levodopa (LD) equivalent dose (LED) was stable from baseline to M6 (1450 mg to 1511 mg). The LDp/CDp base infusion rate increased from 56.1 mg/h LD at baseline to 66.1 mg/h at 1M but was largely stable thereafter (67.9 mg/h at 6M). Over 6M, 15.2% of PwP were treated with LDp/CDp as a monotherapy.

PwP on LDp/CDp showed statistically significant, clinically meaningful, sustained improvements in OFF time (-2.7h), dyskinesia time (-1.7h), MDS-UPDRS III (-5.3), PDSS-2 (-6.0), KPPS (-8.5), and PDQ-39 (-5.3) from baseline to 6M [Figure1, Table 2]. FOGQ and GIDS-PD also significantly improved over 6M of LDp/CDp [Table 2].

Overall, 58 (55.2%) PwP reported at least 1 AE; with hallucination and injection site infection reported by 6% each [Table 3]. Most AEs were mild/moderate (n=18 severe), and 13 AEs were serious. At M6, 30 (29%) PwP discontinued the study, with 9 (8.6%) due to AEs; hallucination was the only AE reported more than once (n=2) as the discontinuation reason.

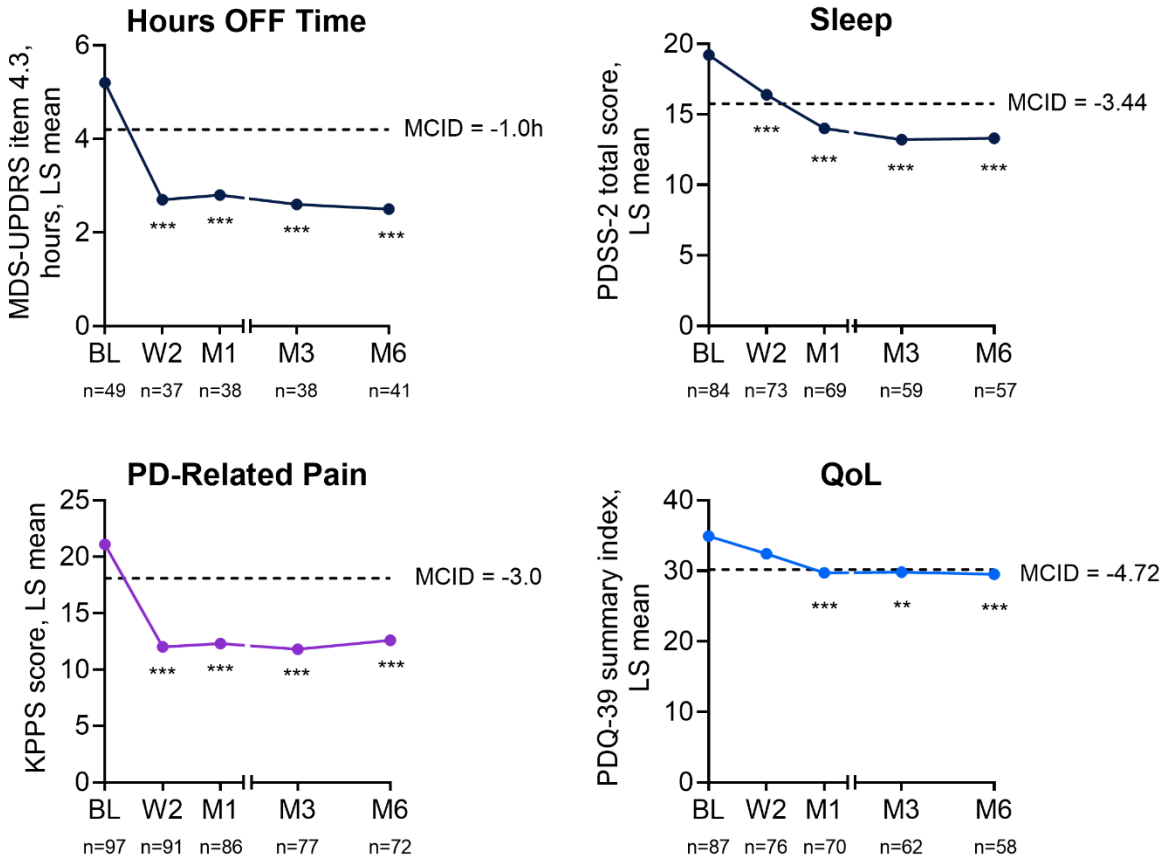
Conclusion: Interim results from the ROSSINI study provide the first real-world data for LDp/CDp, showing improvements in motor fluctuations, non-motor symptoms, and QoL with 6M of treatment. An acceptable safety profile was confirmed in routine clinical practice, with the majority of AEs non-serious, mild to moderate, and manageable.

**Table 1. Baseline Characteristics for First Interim Analysis Population**

| Characteristic | Cohort A (N = 105)[a] |
|---|---|
| Age, years, mean (SD) | 68.5 (9.5) |
| *<65 years, %* | 30.5 |
| *≥65 years, %* | 69.5 |
| Sex, male, % | 56.2 |
| Country, % | |
| *Germany* | 50 |
| *Denmark* | 15 |
| *Sweden* | 13 |
| *Israel* | 11 |
| *Spain* | 6 |
| *Austria* | 3 |
| *Romania* | 2 |
| *Canada* | 1 |
| PD duration, years, mean (SD) | 12.1 (5.3) |
| *<10 years, %* | 39.4 |
| *≥10 years, %* | 60.6 |
| Time since onset of motor fluctuations, years, mean (SD) | 6.4 (5.3) |
| Hoehn and Yahr stage (ON state), mean (SD) | 3.0 (0.9) |
| *≤stage 3, %* | 70 |
| Previous use of device-aided treatment, % | 6 |
| MMSE score, mean (SD) | 27.5 (3.4) |
| OFF time (modified MDS-UPDRS Part IV item 4.3), h, LS mean (SE) | 5.2 (0.5) |
| Dyskinesia time (modified MDS-UPDRS Part IV item 4.1), h, LS mean (SE) | 3.2 (0.4) |
| MDS-UPDRS part II total score, LS mean (SE) | 15.9 (2.0) |
| PDQ-39 summary index score, LS mean (SE) | 34.9 (2.7) |

KPPS, King's Parkinson's Disease Pain Scale; LDp/CDp, foslevodopa/foscarbidopa; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PDQ-39, 39-item Parkinson's Disease Questionnaire; PDSS-2, Parkinson's Disease Sleep Scale-2.

**Figure 1. Key Effectiveness Outcomes After 6 Months with LDp/CDp**




KPPS, King's Parkinson's Disease Pain Scale; LDp/CDp, foslevodopa/foscarbidopa; MCID, minimal clinically important difference; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PDQ-39, 39-item Parkinson's Disease Questionnaire; PDSS-2, Parkinson's Disease Sleep Scale-2. Dashed lines indicate thresholds for meeting defined MCID from baseline.
*P<.05, **P<.01, ***P<.001

**Table 2. Secondary Effectiveness Outcomes with LDp/CDp**

| Outcome | Baseline | Week 2 | Month 1 | Month 3 | Month 6 | CFB to Month 6 |
|---|---|---|---|---|---|---|
| **Dyskinesia time;** modified MDS-UPDRS Part IV item 4.1, h, LS mean | 3.2<br>n=49 | 2.9<br>n=37 | 1.9**<br>n=38 | 2.0**<br>n=39 | 1.5***<br>n=41 | -1.7 |
| **Motor experiences of daily living;** MDS-UPDRS part II total score, LS mean | 15.9<br>n=72 | 13.7**<br>n=64 | 14.4<br>n=58 | 14.4<br>n=53 | 14.8<br>n=52 | -1.1 |
| **Motor symptoms;** MDS-UPDRS part III total score, LS mean | 36.2<br>n=97 | 30.2***<br>n=91 | 32.1**<br>n=81 | 29.3***<br>n=71 | 31.0***<br>n=64 | -5.2 |
| **Freezing of gait;** FOGQ score, LS mean | 12.7<br>n=82 | 10.9**<br>n=71 | 11.4<br>n=68 | 10.0***<br>n=57 | 10.5**<br>n=54 | -2.2 |
| **Generic daytime sleepiness;** ESS score, LS mean | 10.3<br>n=83 | 9.8<br>n=71 | 9.8<br>n=67 | 9.3<br>n=58 | 9.2<br>n=56 | -1.1 |
| **Generic depression;** BDI score, LS mean | 10.7<br>n=72 | 9.7<br>n=64 | 8.4**<br>n=58 | 8.9*<br>n=57 | 10.3<br>n=52 | -0.5 |
| **Generic caregiver burden;** MCSI score, LS mean | 6.9<br>n=38 | 5.3*<br>n=32 | 6.2<br>n=30 | 6.2<br>n=27 | 6.4<br>n=25 | -0.5 |
| **PD-specific gastrointestinal dysfunction;** GIDS-PD score, LS mean | 20.5<br>n=84 | 18.8<br>n=72 | 18.1<br>n=67 | 16.9*<br>n=58 | 16.3**<br>n=54 | -4.3 |

BDI, Beck Depression Inventory; ESS, Epworth Sleepiness Scale; FOGQ, Freezing of Gait Questionnaire; GIDS-PD, Gastrointestinal dysfunction in PD scale; LDp/CDp, foslevodopa/foscarbidopa; LS, least squares; MCSI, Modified Caregiver Strain Index; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PDQ-39, 39-item Parkinson's Disease Questionnaire.
*$P$< .05, **$P$<.01, ***$P$<.001

**Table 3. Adverse Events**

| | N=105<br>n, (%) |
|---|---|
| Any AE | 58 (55.2) |
| AE with reasonable possibility of being related to study treatment | 43 (41.0) |
| AE with reasonable possibility of being related to study device | 21 (20.0) |
| AE that is considered associated with product complaint | 12 (11.4) |
| Severe AE | 18 (17.1) |
| Serious AE | 13 (12.4) |
| AE leading to treatment withdrawal | 9 (8.6) |
| Deaths[a] | 2 (1.9) |
| AEs occurring in ≥3% of patients | |
| Hallucination | 6 (5.7) |
| Injection site infection | 6 (5.7) |
| Abscess | 4 (3.8) |
| Anxiety | 4 (3.8) |
| Skin infection | 4 (3.8) |
| Skin reaction | 4 (3.8) |
| Infusion site cellulitis | 3 (2.9) |
| On and off phenomenon | 3 (2.9) |
| Serious AEs occurring in ≥2 patients | |
| Abdominal wall abscess | 2 (1.9) |
| Hallucination | 2 (1.9) |

AE, adverse event.

[a]One was due to suspected porphyria, exacerbated by metamizole, aspiration pneumonia; the other was due to lymphoma, pleural effusion.

## LBA-16: Intracerebroventricular administration of anaerobic dopamine in Parkinson's disease patients with L-dopa-related complications

*D. Devos; P. Odou; J. Labreuche; G. Touzet; N. Reyns; A. Duhamel; C. Leclercq; T. Ouk; K. Dujardin; L. Carton; A. Rolland; D. Deplanque; V. Foutel; M. Fisichella; C. Moreau (Lille, Haute de France, France)*

Objective: To investigate the safety and efficacy of continuous circadian and personalized intracerebroventricular administration of anaerobic dopamine (A-dopamine) in patients with Parkinson's disease at the L-dopa-related complications (LDRC) stage.

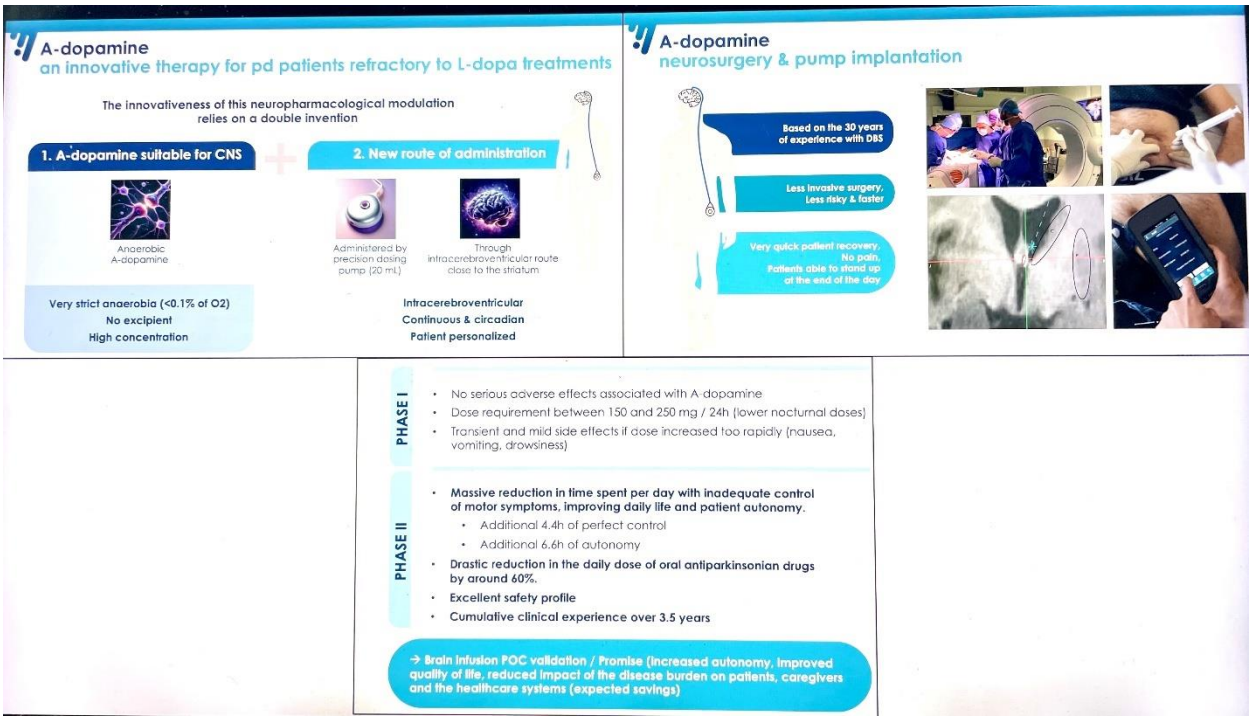
Background: L-dopa leads to LDRC such as dyskinesia and motor fluctuation in 50% of patients after 5 years forcing to a change in its administration route to cope with these PK/PD drawbacks. Dopamine does not cross the digestive and brain blood barriers and is rapidly oxidized. The new concept of A-dopamine, specifically designed for a direct CNS use, has proved safe and efficacious in two mouse models and one chronic non-human primate model.

Methods: A phase 1 study of A-dopamine titration with concomitant reduction of oral dopaminergic therapy was followed by a randomized, controlled, open-label, crossover phase 2 study comparing an A-dopamine treatment on top of an optimized oral antiparkinsonian therapy to an optimized oral antiparkinsonian therapy alone over a month. Patients were then able to continue A-dopamine over the long term. The primary endpoint in phase I was safety, and the primary endpoint in phase 2 was the blinded assessment of percentage over target (i.e., off and dyskinesia), recorded by actimetry at home using a wristwatch. Secondary endpoints included the fluctuations and dyskinesias on two-week home diaries, dyskinesia and MDS-UPDRS scales, safety and behavior using neuropsychological and psychiatric examinations.

Results: No serious adverse reactions induced by A-dopamine was observed in 12 patients.

The primary criterion was significantly reduced on A-dopamine compared with oral treatment. The mean number of hours gained in the time to ‘on’ without dyskinesia was 4.4h (i.e. perfect control) and 6.6h of time with perfect or slight off or slight dyskinesia with 60% reduction in the daily dose of oral antiparkinsonian drugs. Patients wished to continue their treatment over the long term, with maintenance of benefit and absence of serious dopamine- or device-related adverse events with a maximum follow-up of 4.5 years. Long-term safety is excellent, MRI monitoring didn’t reveal any structural changes.

Conclusion: This study demonstrates promising results of this new dopamine for cerebral use, which will now be the subject of an international pivotal Phase III trial. Importantly, clinical data showed a different effect of A-dopamine from that of L-dopa, notably with no A-dopamine-induced dyskinesia.




**LBA-17: TEMPO-4: A Phase 3 Open-Label Trial to Investigate the Safety and Efficacy of Long-term Administration of Tavapadon in People With Parkinson's Disease**

*R. Pahwa; R. Dhall; Z. Mari; A. Tarakad; C. Oehlwein; R. Sanchez; S. Duvvuri; I. Chang; J. Boiser; C. Zadikoff (Kansas City, KS, USA)*

Objective: To evaluate the long-term safety and efficacy of tavapadon in adults with Parkinson's disease (PD).

Background: Tavapadon, an oral, once-daily, selective D1/D5 agonist, demonstrated efficacy with a favorable safety profile over 27 weeks of treatment in phase 3 trials in adults with early PD (<3 years' disease duration; TEMPO-1 [NCT04201093], TEMPO-2 [NCT04223193]), and PD with motor fluctuations (≥2.5 hours of daily OFF time; TEMPO-3 [NCT04542499]). Here, we report an interim analysis from the TEMPO-4 trial (NCT04760769).

Methods: TEMPO-4 is a phase 3, open-label trial of tavapadon in participants who completed the previous TEMPO-1, TEMPO-2, or TEMPO-3 trials, as well as de novo participants with PD (modified Hoehn and Yahr stage 1, 1.5, 2, 2.5, or 3) on a stable dose of levodopa. Participants received tavapadon (5 to 15 mg QD) for up to 58 weeks (85 total weeks of exposure for active rollover participants), followed by a 10-day safety/withdrawal assessment period, and a 20-day safety follow-up period.

Results: TEMPO-4 enrolled 992 participants with PD, including 468 participants rolled over from the active tavapadon arms in the TEMPO-1, -2, and -3 trials, and 524 previously untreated participants (placebo rollover, n=471; de novo, n=53). As of October 25, 2024, 484 (48.8%) participants completed the study, 285 (28.7%) discontinued treatment, and treatment was

ongoing for 223 (22.5%). The most common reasons for treatment discontinuation were adverse events (AEs; n=136 [13.7%]) and withdrawal by subject (n=71 [7.2%]). The safety profile of tavapadon was consistent with prior studies; the majority of AEs were non-serious and mild to moderate in severity [table1]. No new safety signals were identified, including vital signs or laboratory/electrocardiogram findings. Active rollover participants had stable motor improvements with continued tavapadon treatment. Placebo rollover and de novo participants showed improvements in motor function, which remained stable with continued treatment.

Conclusion: This interim analysis from the TEMPO-4 trial demonstrates that tavapadon has a favorable long-term safety profile and stable efficacy with continued treatment. Low rates of AEs of interest support a potential differentiated approach of selective D1/D5 agonism relative to available dopaminergic therapies.

**Table.** Summary of Adverse Events (Full Analysis Set)

| | Tavapadon 5-15 mg QD | | |
|---|---|---|---|
| | Placebo rollover and de novo participants (previously untreated participants) N=523 | Active rollover participants (previously treated with tavapadon) N=468 | Overall N=991[a] |
| TEAE, n (%) | 419 (80.1) | 327 (69.9) | 746 (75.3) |
| Mild | 148 (28.3) | 144 (30.8) | 292 (29.5) |
| Moderate | 207 (39.6) | 153 (32.7) | 360 (36.3) |
| Severe | 64 (12.2) | 30 (6.4) | 94 (9.5) |
| TEAE related to study drug,[b] n (%) | 286 (54.7) | 164 (35.0) | 450 (45.4) |
| Serious TEAE, n (%) | 52 (9.9) | 27 (5.8) | 79 (8.0) |
| TEAE leading to study drug discontinuation, n (%) | 100 (19.1) | 40 (8.5) | 140 (14.1) |
| Death, n (%) | 2 (0.4) | 2 (0.4) | 4 (0.4)[c] |
| TEAEs with incidence ≥5%, n (%)[d] | | | |
| Nausea | 87 (16.6) | 22 (4.7) | 109 (11.0) |
| Dizziness | 72 (13.8) | 35 (7.5) | 107 (10.8) |
| Headache | 74 (14.1) | 21 (4.5) | 95 (9.6) |
| Fall | 57 (10.9) | 34 (7.3) | 91 (9.2)[e] |
| COVID-19 | 39 (7.5) | 51 (10.9) | 90 (9.1) |
| Constipation | 39 (7.5) | 16 (3.4) | 55 (5.5) |
| Safety topics of special interest,[d] n (%) | | | |
| Nausea | 95 (18.2) | 23 (4.9) | 118 (11.9) |
| Headache | 77 (14.7) | 22 (4.7) | 99 (10.0) |
| Fall | 57 (10.9) | 34 (7.3) | 91 (9.2) |
| Hallucination | 43 (8.2) | 19 (4.1) | 62 (6.3) |
| Somnolence | 25 (4.8) | 23 (4.9) | 48 (4.8) |
| Hypotension | 27 (5.2) | 14 (3.0) | 41 (4.1) |
| Orthostatic hypotension | 19 (3.6) | 18 (3.8) | 37 (3.7) |
| Impulse control disorders | 10 (1.9) | 4 (0.9) | 14 (1.4) |

[a]One participant did not receive any tavapadon treatment before discontinuation. [b]As assessed by investigator. [c]All deaths were assessed as unrelated to tavapadon. [d]Differences in incidence of TEAEs and safety topics of interest are due to differences in search strategy, with TEAE incidence based on preferred term, and incidence of safety topics of interest based on custom MedDRA queries. For example, the safety topic of interest "Headache" may also include TEAEs of tension headache or cluster headache. [e]The majority of falls were nonserious and not related to tavapadon. QD, once daily; REM, rapid eye movement; TEAE, treatment emergent adverse event.

## LBA-18: Serum α-Synuclein Seeding as a Non-Invasive Biomarker for Early Parkinson's Disease: Linking Central Pathology to Peripheral Propagation

*Y. Kuang; H. Mao; P. Xu (Guangzhou, Guangdong, People's Republic of China)*

Objective: To investigate whether the serum α-synuclein (α-Syn) seed amplification assay (SAA) can serve as a non-invasive biomarker for early Parkinson's disease (PD), and to explore the underlying mechanisms contributing to peripheral α-Syn seed propagation.

Background: Early diagnosis of PDremains a major clinical challenge due to the absence of sensitive and mechanistically informative biomarkers. Although isolated REM sleep behavior disorder (iRBD) is a well-established prodromal stage of PD, it remains unclear whether pathological α-Syn seeds can be detected in the peripheral blood of these individuals.

Methods: We conducted α-synuclein (α-Syn) preformed fibril (PFF) injections in both young and aged mouse models, alongside clinical serum analyses from iRBD patients. Serum α-Syn seed amplification assay (SAA) parameters, including F_max and PAR, as well as serum S100 levels—a peripheral marker of blood-brain barrier (BBB) integrity—were measured. Lysosomal function, inflammation, and BBB integrity were assessed.

Results: In aged mice, peripheral α-Syn seeds were detected as early as two months post-injection, preceding motor symptoms and associated with increased brain α-Syn aggregation and microglia-driven BBB disruption. These mice also showed reduced TPP1 levels, suggesting age-related lysosomal dysfunction. TPP1 overexpression rescued lysosomal clearance capacity and reduced α-Syn pathology. In the iRBD cohort, serum α-Syn SAA signals strongly correlated with elevated S100 levels ($r = 0.68–0.71$, $p < 0.01$), indicating concurrent BBB disruption despite the absence of clinical symptoms.

Conclusion: Our study demonstrates that serum α-Syn seeds reflect early central PD pathology, especially in the context of aging. Integrating α-Syn SAA with BBB–associated markers may improve early diagnosis of PD in at-risk populations such as individuals with iRBD.

**LBA-19: Longitudinal Changes in Motor, Cognitive, and Functional Outcomes in REM Sleep Behavior Disorder and the Predicted Sample Sizes for Future Clinical Trials**

*C. Xiong; H. Hang; H. De La Cruz; A. Avidon; D. Bliwise; M. Campbell; S. Criswell; A. Davis; K. Duff; K. Ehgoetz-Martens; J. Elliott; T. Ferman; J. Fields; L. Forsberg; J.F. Gagnon; Z. Gan-Or; M. Howell; M. Hu; X. Hu; D. Huddleston; K. Kantarci; P. Kotzbauer; J. Langley; M. Lim; J. Locke; V. Lowe; S. McCarter; J. McLeland; M. Miglis; E. Mignot; T. Miyagawa; L. Neilson; K. Nichols; A. Pelletier; O. Ross; C. Schenck; W. Singer; E. St. Louis; O. Sum-Ping; L.M. Trotti; A. Videnovic; Y. Ju; B. Boeve; R. Postuma (St. Louis, MO, USA)*

Objective: To estimate rates of longitudinal change in MDS-UPDRS-motor (Part III), Clinical Dementia Rating Sum of Boxes (CDRSUM), Prodromal Synucleinopathy Rating Scale (PSRS), and Montreal Cognitive Assessment (MoCA), and predict sample sizes needed for future clinical trials on REM sleep behavior disorder (RBD).

Background: Background: RBD Clinical trials must identify at least 1 primary efficacy endpoint, a difficult task considering RBD's clinical heterogeneity. Endpoints assessing multiple domains including motor, cognitive, and functional changes may lead to better estimates of RBD progression and hence smaller sample sizes for future clinical trials.

Methods: We analyzed longitudinal data of up to 2.95y of MoCA (n=379), PSRS (n=268), CDRSUM (n=363), and MDS-UPDRS (n=358) in the ongoing North American Prodromal Synucleinopathy Consortium (NAPS; NIH R34AG056639, U19AG071754), a 9-site observational study to assess patients with polysomnogram-confirmed RBD. Longitudinal trajectories were estimated by random intercept and random slope models on z-scores of each outcome. The estimated rates of change and associated between- and within-subject variances were then used to project the sample sizes needed for a future 1:1 clinical trial to detect a range of effect sizes.

Results: Results: RBD participants exhibited annual increases (in z-scores) in PSRS (slope=0.2191/y, SE=0.0314/y; p<0.0001), CDRSUM (slope=0.113/y, SE=0.0201 /y; p<0.0001), and MDS-UPDRS (slope=0.1341/y, SE=0.018/yr; p<0.0001). To detect a 50% to 30% reduction in the rate of change by a treatment arm with at least 80% power in a future 2-y 1:1 clinical trial with semi-annual assessments on RBD, the minimum number of patients to be enrolled is from 292 to 808, 896 to 2486, and1548 to 4296 when PSRS, MDS-UPDRS, and CDRSUM are used as primary efficacy endpoints, respectively. MoCA showed a small but statistically significant increase over time (slope=0.0281/y, SE=0.0124/y; p=0.0235).

Conclusion: Conclusions: PSRS assesses multiple domains, including cognitive, neuropsychiatric, motor-axial, motor-appendicular, autonomic, sleep, and sensory symptoms, which results in a smaller sample size needed to demonstrate efficacy compared with scales that assess a single domain and may serve as an optimal efficacy endpoint in future clinical trials in RBD.

**LBA-20: Glovadalen, a D1 Receptor Positive Allosteric Modulator for People With Parkinson's Who Experience Significant Daily Motor Fluctuations: A Phase II, Double-Blind, Randomized Trial**

*M. Biagioni, R. Nicholl, T. Bornemann, C. Legendre, S. Leach, H. Naik, A. el Baghdady, N. Williamson, A. Benoit, D. Menshykau, L. Vroye (Braine-l'Alleud, Walloon Brabant, Belgium)*

Objective: ATLANTIS (NCT06055985), a Phase II proof of concept study, assessed the efficacy, safety and tolerability of oral glovadalen (UCB0022) in people living with Parkinson's disease who experience significant daily motor fluctuations. This is the first reporting of ATLANTIS and first efficacy data from glovadalen in people with Parkinson's disease.

Background: Glovadalen is an orally available, brain-penetrant positive allosteric modulator of the D1 receptor that selectively enhances D1 signaling only when and where dopamine is released. The D1 receptor selectivity and the allosteric mechanism of action of glovadalen reduces the risk of receptor overstimulation and offtarget signaling, thereby decreasing the likelihood of associated adverse events (AEs) that typically accompany current dopaminergic treatments. In a Phase I, randomized, first-in-human study (NCT04867642), glovadalen demonstrated an acceptable safety and tolerability profile (no deaths, serious treatment-emergent AEs [TEAEs] or TEAEs of severe intensity).

Methods: ATLANTIS was a Phase II, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Eligible participants were aged 35–85 years, in ON state Hoehn and Yahr Stages 1–3, with a Parkinson's disease diagnosis for ≥5 years, experiencing significant daily motor fluctuations, and receiving oral levodopa combination therapy with or without oral adjunctive anti-parkinsonian therapies. Participants (N=207) were randomly assigned (1:1:1) to receive one of two different doses of glovadalen (low-dose, n=70; high-dose, n=67) or placebo (n=70) as adjunctive to optimized standard of care for 10 weeks. The primary endpoint was the change in the average number of hours of OFF time (Hauser diary) from Baseline to Day 70. Secondary endpoints included safety, tolerability and pharmacokinetics.

Results: In the ATLANTIS study, glovadalen met the primary endpoint demonstrating superiority over placebo in the change from Baseline to Day 70 in the average number of OFF hours per day. Glovadalen had a positive safety profile and was well tolerated. There were no notable differences in the incidence of dopaminergicrelated TEAEs between treatment groups. More than 40% of participants in the active treatment arms reported feeling 'much better' or 'somewhat better' on the Patient Global Impression of Change of PD symptoms, versus 22% in the placebo group. The study was well conducted with a very low discontinuation rate (9% placebo, 7% low-dose and 6% high-dose). Drug exposure followed the predicted pattern observed in Phase I healthy volunteer studies. The proof-of-concept ATLANTIS study provides proof of mechanism for glovadalen as a selective D1 PAM, improving OFF time in participants with Parkinson's who experience significant daily motor fluctuations without notable worsening of dopamine-related TEAEs or dyskinesias.

**LBA-21: A Phase III, pivotal trial of staged, bilateral magnetic resonance-guided focused ultrasound pallidothalamic tractotomy for motor complications in Parkinson's disease**

*M. Cruz Rodríguez-Oroz, A. Dalvi, L. Zucker, W.C. Chang, P. Wu, M. Kaplitt, H. Sarva, H. Eisenberg, P. Fishman, V. Buch, M. Matarazzo, M. del Alamo, S. Sani, M. Pourfar, A. Mogilner (Pamplona, Spain)*

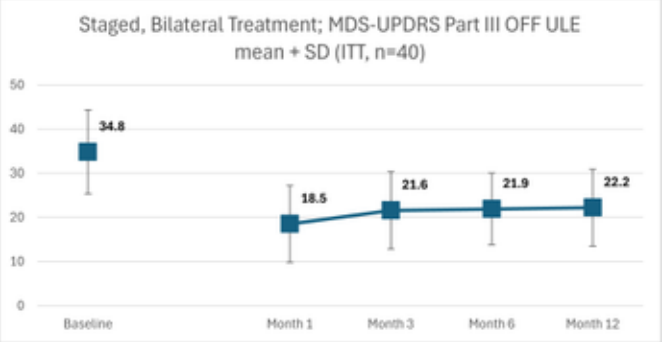
Objective: To evaluate the safety and efficacy of staged, bilateral magnetic resonance-guided focused ultrasound (MRgFUS) pallidothalamic tractotomy (PTT) in patients with Parkinson's disease (PD) experiencing motor complications.

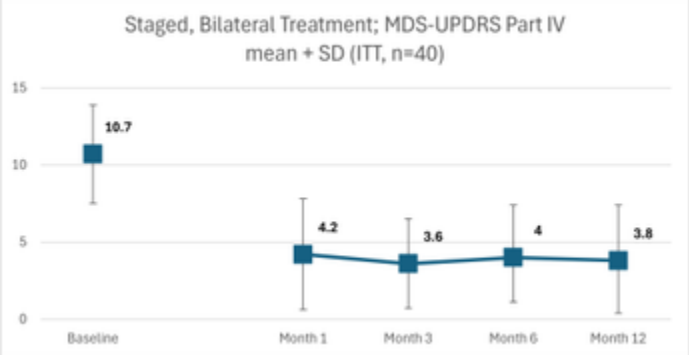
Background: As Parkinson's disease progresses, dyskinesia and motor fluctuations emerge and further often emerge develop despite optimized medical therapy, leading to reduced quality of life. MRgFUS is a precise, incisionless technique that enables precise targeting of the pallidothalamic tract at the H1/Field of Forel, offering a novel alternative for PD patients with motor complications. This study investigates theoutcomes of staged, bilateral MRgFUS PTT in a multicenter, phase III trial.

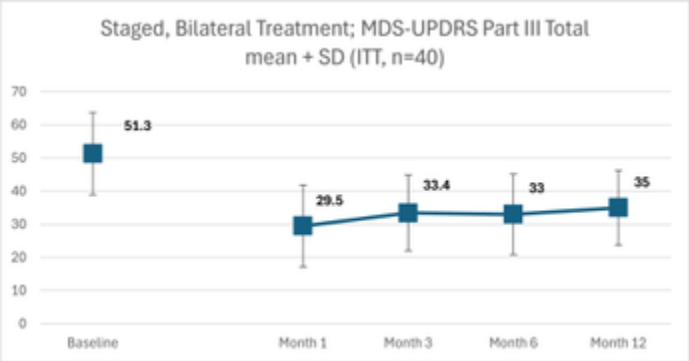
Methods: This prospective, open-label, single-arm trial (NCT04728295) enrolled 84 subjects across nine international centers. Eligible participants (≥30 years old) with PD and motor complications underwent unilateral MRgFUS PTT, followed by staged, bilateral treatment at least 6 months later, if eligible. Primary efficacy was assessed by change in MDS-UPDRS Part III OFF (bilateral upper and lower extremity score) at 3 months after staged, bilateral treatment.

Secondary outcomes included MDS-UPDRS Part IV and Part III OFF total scores. Safety was evaluated through treatment-emergent adverse events.

Results: Fifty-four subjects received unilateral MRgFUS PTT; 40 proceeded to staged, bilateral treatment. At 3 months post-unilateral treatment, MDS-UPDRS Part III OFF (upper and lower extremity score, treated side) improved by 50% (20.9 ± 5.3 to 10.0 ± 5.4), and Part IV improved by 56.3% (10.5 ± 3.5 to 4.6 ± 3.7). Following staged, bilateral treatment, MDS-UPDRS Part III OFF (upper and lower extremity score, bilateral) improved by 33.9%, and Part III OFF total scores improved by 32% (51.3 ± 12.4 to 33.4 ± 11.4). Part IV scores improved by 68.1% (10.7 ± 3.2 to 3.6 ± 2.9). Those two outcomes were statistically significant ($p<0.0001$). Improvements were sustained through 12 months post-bilateral procedure. Adverse events were mostly mild or moderate. After unilateral treatment, 30 related events occurred in 21 subjects (87% mild, no severe) and 60% resolved within 6 months; after bilateral treatment, 43 events occurred in 22 subjects (70% mild, 2% severe) and 40% resolved within 12 months. Most common related events included imbalance, dysarthria, and fatigue. These results may help to guide clinicians and patients as to selection and expectation for those who may choose this procedure.






**LBA-22: First Clinical Trials of ARV-102, a PROTAC LRRK2 Degrader: Characterization of Pathway Engagement in Healthy Volunteers and Patients With Parkinson's Disease**

*L. Smits; C. Woodward; S. Aksenov; A.L. Costa Zaninotto; C. Donnelly; T. Storz; C. Lubeski; M. MacDougall; K. Kelly; A. Hendricson; K. Fraser; S. Korsten; P. Kremer; A. Cacace; I. Conti; P. Montenigro (Leiden, Netherlands)*

Objective: To assess downstream effects of leucine-rich repeat kinase 2 (LRRK2) degradation by ARV-102, a potent PROteolysis TArgeting Chimera (PROTAC), in healthy volunteers (HVs) and evaluate the safety, pharmacokinetics (PK), and pharmacodynamics of single doses of ARV-102 in an ongoing phase 1 study (EUCT 2024-516888-84-00) in patients (pts) with Parkinson's disease.

Background: LRRK2 modulates clinical features of Parkinson's disease, and mutations are a cause of late-onset disease. In a phase 1 study in HVs, single and multiple oral doses of ARV-102 were well tolerated, showed exposure increases with dose escalation, and substantially reduced LRRK2 protein levels in peripheral blood mononuclear cells (PBMCs) and cerebrospinal fluid (CSF).

Methods: Unbiased proteomic analyses were conducted on CSF samples from ARV-102-treated HVs to assess ARV-102-induced changes in LRRK2-associated proteins. A single-center, double-blind, randomized, phase 1 study is evaluating a single oral dose of ARV-102 (50 or 200 mg administered 3:1 vs placebo) in pts with Parkinson's disease. Primary objective is to evaluate ARV-102 safety and tolerability, secondary objective is to characterize ARV-102 plasma PK, and an exploratory objective is to evaluate pharmacodynamic effects of ARV-102.

Results: Proteomic analyses using CSF from HVs treated with 80-mg doses of ARV-102 daily for 14 days (n=9) showed decreases (mean % of baseline) in lysosomal (78.5% cathepsin H, 71.4% GPNMB, and 78.5% granulin) and microglial (85.9% C1QTNF1, 84.8% ENTPD1, and 46.8% CD68) pathway markers known to be elevated in LRRK2 Parkinson's disease, indicating ARV-102 regulates pathways linking LRRK2 to neurodegenerative disease. In the phase 1 study, 19 pts with Parkinson's disease received a single dose of ARV-102 or placebo (50-mg cohort: n=12; 200-mg cohort: n=7). Median reductions in LRRK2 protein levels from baseline in PBMCs were -86% in the 50-mg cohort and -97% in the 200-mg cohort, consistent with dose-dependent

peripheral LRRK2 degradation seen in HVs. In addition, ARV-102 was well tolerated at both dose levels; treatment-related adverse events (AEs) of headache, diarrhea, and nausea were mild, and there were no serious AEs. ARV-102 exposure (AUCinf and Cmax) increased in a dose-dependent manner in plasma and in CSF, indicating brain penetration. The safety profile and exposure levels of ARV-102 in pts with Parkinson's disease were consistent with findings from HVs. Evaluation of multiple doses of ARV-102 in pts with Parkinson's disease, including assessment of LRRK2 and downstream pathway engagement, is ongoing