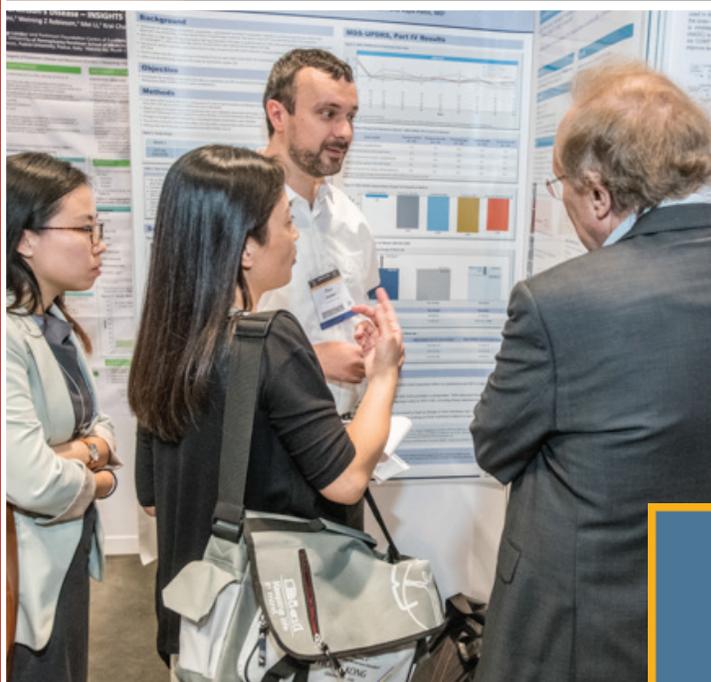


# LATE-BREAKING ABSTRACTS

International Congress of Parkinson's  
Disease and Movement Disorders®



August 27-31, 2023  
Copenhagen  
**DENMARK**



International Parkinson and  
Movement Disorder Society

# International Congress of Parkinson's Disease and Movement Disorders®

## 2023 Late-Breaking Abstracts

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### **LBA-1: Bi-allelic variants in HCRT cause autosomal recessive narcolepsy**

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### **LBA-2: Olfactory mucosa RT-QuIC in combination with olfactory function as a biomarker for Parkinson's disease**

Pham, N., Kwak, I-H., Ma, H-I., Kim, Y. (*Anyang, Korea*)

### **LBA-3: Identification of over 45 leucine-rich repeat kinase 2 (LRRK2) activating variants**

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Calvo-Flores Guzman, B., Perez, N., Garcia-Collazo, A., Cubero, E., Barril, X., Bellotto, M., Taylor, J., (Ticino, Switzerland)

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Satolli, S., Petrucci, A., Bruno, G., Capacci, E., Casali, C., Ceravolo, R., De Micco, R., De Michele, G., Ferrari, C., Filla, A., Fini, N., Govoni, A., Lopergolo, D., Malandrini, A., Mignarri, A., Musumeci, O., Pellecchia, M.T., Perna, A., Ravenni, R., Ricca, I., Rossi, S., Rufa, A., Silvestri, G., Tessitore, Pellerin, D., Brais, B., Santorelli, FM. (Pisa, Italy)

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Frank, S. (Boston, MA, USA)

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**LBA-20: One-year blinded follow-up of posterior subthalamic stimulation for arm tremor: Secondary endpoints of a randomized controlled crossover trial**

Skogseid, I., Konglund, A.E., Reich, M.M., Pripp, A.H., Dietrichs, E., Volkmann, J., Skogseid, I.M. (Oslo, Norway)

# 2023 INTERNATIONAL CONGRESS LATE-BREAKING ABSTRACTS

## **LBA-1: Bi-allelic variants in HCRT cause autosomal recessive narcolepsy**

Hakami, W., Alshahwan, S., Alkuraya, F., Tabarki, B. (*Riyadh, Saudi Arabia*)

**Objective:** To gain further insight into the HCRT-related narcolepsy, we present findings on five additional patients from two unrelated families who share a homozygous truncating variant in this gene. This is the second reported cases. There is only one previously reported case with this gene without delineation of the clinical presentation, investigation and outcome.

**Background:** Narcolepsy with cataplexy, also known as narcolepsy type 1 or NT1, is a sleep disorder characterized by excessive daytime sleepiness, hypnagogic hallucinations, sleep paralysis, and cataplexy (loss of muscle tone triggered by strong emotions). It is caused by a deficiency in the hypothalamic neuropeptide hypocretin/orexin.<sup>1</sup> The underlying mechanism of the disease remains unknown. However, currently available data support an immune-related mechanism that leads to the loss of hypocretin-producing neurons. Furthermore, it has been shown that environmental risk factors and genetic variations at multiple loci are associated with NT1. The HCRT gene encodes hypocretin/orexin, and thus far, the only phenotype documented under this gene in OMIM is a tentative link to autosomal dominant narcolepsy initially proposed by Peyron et al who described a single patient with a heterozygous missense HCRT variant.

**Method:** All affected individuals were ascertained through patient care and had been evaluated for narcolepsy with cataplexy with next-generation sequencing techniques in a clinical context. Clinical data, brain MRI, EEG recordings, and laboratory tests were retrieved from medical records retrospectively.

### **Results: Results**

We evaluated five patients from two seemingly unrelated consanguineous Saudi families. The key characteristics of these patients are summarized in Table 1 and figure 1. Through whole exome sequencing, we identified a shared homozygous variant (NM\_001524.1:c.17\_18del; p.(Thr6Lysfs\*?)) of HCRT in all five patients. Sanger sequencing confirmed the presence of this variant as homozygous in all affected individuals and as heterozygous or absent in the available unaffected family members who underwent testing.

Clinically, our patients presented with the clinical features of cataplexy: episodes, characterized by spells of axial atonia and preserved consciousness. These spells were typically triggered by strong emotions, as depicted in Video 1. The attacks began at 3 to 4 months of age, lasting between 10 and 50 seconds and occurring up to 12 times per day. Neurological examination conducted between spells yielded unremarkable findings. The onset of excessive daytime sleepiness occurred around the median age of 6 months, with episodes lasting up to 40 min and recurring two to three times daily. Initially, two patients exhibited mild motor delay. EEG and brain MRI results were normal. Measurement of hypocretin-1 levels in cerebrospinal fluid using direct radioimmunoassay indicated marked reduction with levels below < 90 pg/mL (normal > 200 pg/mL). As for follow-up, the parents declined any treatment. Over time, cataplexy significantly improved in all patients: two patients experienced complete resolution of spells by the age of 2 years, one patient by the age of 4 years, and the remaining two patients showed

significant improvement. In terms of narcoleptic episodes, two patients achieved complete recovery, one patient demonstrated significant improvement, and two patients showed mild improvement. Developmental milestones were normal for all patients; except for one patient who displayed mild motor delay (though still at a young age (15 months)).

## Discussion

We present a case series of five patients from two consanguineous families, each harboring a novel homozygous variant of HCRT. All affected individuals exhibited severe cataplexy accompanied by narcolepsy symptoms during infancy.

Narcolepsy type 1 is characterized by a deficiency in the hypothalamic neuropeptide HCRT. The precise pathological mechanism responsible for the loss of hypocretin neurons in most narcolepsy patients with cataplexy remains largely unknown. However, the strong association between the HLA-DQB1\*06:02 allele, polymorphisms in other immune-related genes, and the immunological-autoimmune response observed in narcolepsy patients with cataplexy supports the autoimmune hypothesis.<sup>4,5</sup>

Orexins, also known as hypocretins, are peptide neurotransmitters expressed in a specific population of neurons within the lateral hypothalamus of the mammalian brain. Postmortem examination of hypothalamic tissue from narcolepsy patients revealed a significant reduction in HCRT transcription level, suggesting the destruction of HCRT-producing neurons in narcolepsy.<sup>6</sup> These orexins are derived from a common precursor protein, prepro-orexin, through proteolysis, resulting in two isoforms: orexin-A and orexin-B. The HCRT gene, located on chromosome 17q21-q24, consists of two exons and one intron and encodes a 131-amino-acid precursor polypeptide. Initially, HCRT involvement in NT1 was only identified in a single patient; with dominant inheritance.<sup>3</sup> In 2019, we briefly described the family of three children as part of a large cohort of “confirmatory” cases.<sup>7</sup> However, OMIM still lists autosomal dominant narcolepsy as the only phenotype linked to HCRT. This prompted us to expand the description of the first family and to add another unpublished family that shared the same founder homozygous variant. The fact that this founder variant is truncating and presumptive loss of function is interesting because homozygous Hcrt knockout mice displayed a phenotype remarkably similar to that observed in human narcolepsy patients.<sup>8</sup> Furthermore, a genome-wide association study identified an association between narcolepsy with cataplexy and a specific nucleotide polymorphism (SNP) (rs2305795) located in the untranslated region (3'UTR) of the purinergic receptor subtype P2RY11 gene on chromosome 19p13.2.<sup>4</sup> It is worth noting that genetic causes of cataplexy have been identified in patients with variants in KCNMA1, KIF1A, or NPC1/NPC2. In such cases, cataplexy is often accompanied by developmental delay and epilepsy

**Conclusion:** Genetic testing of the HCRT gene should be conducted in specific subgroups of NT1, particularly those with early onset, familial cases, and a predominantly cataplexy phenotype.

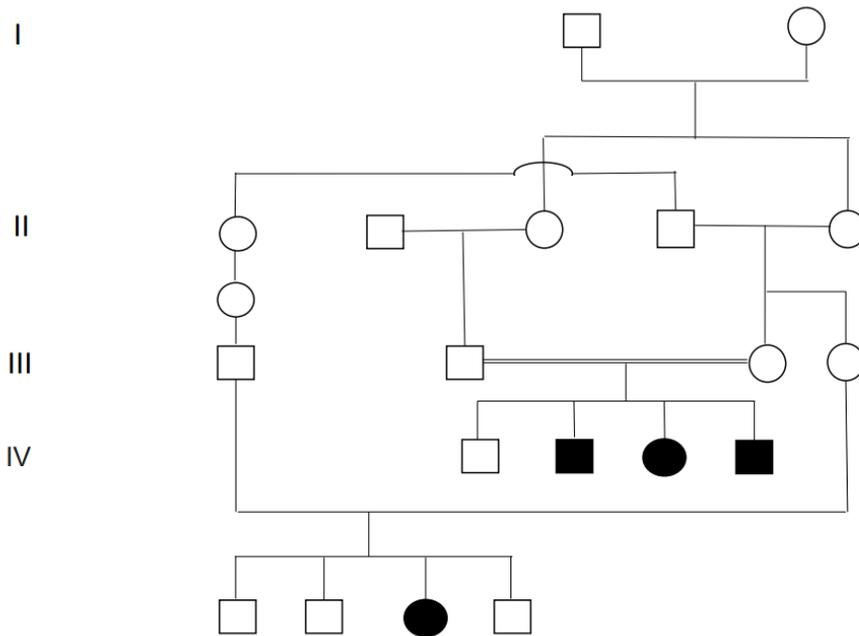


Figure 1: Family pedigree of first and second family showing four affected children.

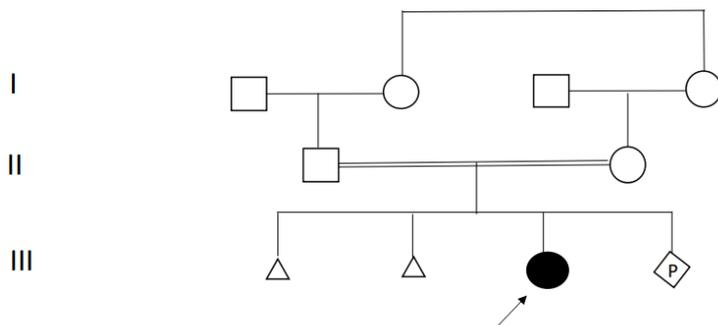


Figure 2: Family pedigree showing 1 affected child .The index case is indicated by an arrow.

**LBA-2: Olfactory mucosa RT-QulC in combination with olfactory function as a biomarker for Parkinson's disease**

Pham, N., Kwak, I-H., Ma, H-I., Kim, Y. (Anyang, Korea)

**Objective:** We aimed to enhance the distinction between patients with Parkinson's disease (PD) and non-PD controls by combining real-time quaking-induced conversion (RT-QuIC) assay using olfactory mucosa (OM) with clinical data on olfactory function.

**Background:** The presence of alpha-synuclein aggregation in neurons of olfactory epithelium has been adopted for RT-QuIC assay, which took advantage of peripheral tissues for a less invasive diagnosis. Besides that, hyposmia is also a common symptom during the early stages of PD. Therefore, incorporating OM RT-QuIC and olfactory function assessments may improve the specificity and sensitivity of the diagnosis.

**Method:** We collected olfactory epithelium samples from individuals with early-stage PD patients (n=10) and non-PD controls (n=10). To ensure applicability in real-world clinical settings, the controls were defined as individuals with parkinsonism whose nigrostriatal dopaminergic nerve terminals were preserved according to PET image, indicating that symptoms were caused by other factors or pre-stage of nigrostriatal degeneration. The ability to induce a-synuclein aggregation of OM samples seeded with human recombinant alpha-synuclein was assessed using RT-QuIC assay. All participants were evaluated by Hoehn and Yahr scale, MDS-UPDRS, and olfactory function tests (YSK olfactory function test).

**Results:** Non-PD controls were older than patients with PD patients (64.0 versus 55.6, P=0.02). The OM RT-QuIC assay distinguished patients with PD from non-PD controls with 70.0% sensitivity (95% confidence interval [CI], 34.8-93.3) and 60.0% specificity (95% CI, 26.2-87.8). Additionally, total score of olfactory function test was not different between PD and control (19.45 versus 19.28, P=0.96). Olfactory function test was not different between the PD patients with negative and positive RT-QuIC results (total olfactory score 20.3 versus 19.1, P=0.77). This trend was also observed among non-PD controls according to RT-QuIC results (18.5 versus 19.6, P=0.89).

**Conclusion:** The combination of olfactory function and RT-QuIC assay using olfactory epithelium did not yield satisfactory results in differentiating PD patients from non-PD controls. However, it is important to note that our non-PD controls were not healthy individuals; they were significantly older than PD patients and may have had subclinical degenerative disorders, which could have influenced the RT-QuIC results. In addition, PD patients were in early stage of the disease, therefore longitudinal observation may clear their diagnosis. To validate the significance of our findings, a larger sample size is necessary.

### **LBA-3: Identification of over 45 leucine-rich repeat kinase 2 (LRRK2) activating variants**

Sammler, E., Pratusевичute, N., Gomes, S., Black, K., Morel, G., Borsche, M., Alcalay, R., Huin, V., Zittel, S., Madoev, H., Tonelli, F., Wightman, M., Zimprich, A., Alessi, D., Klein, C., Lohmann, K. (*Dundee, United Kingdom*)

**Objective:** Here, we present an analysis pipeline for annotating the functional impact of leucine-rich repeat kinase 2 (LRRK2) variants identified in Parkinson's disease (PD) patients in terms of LRRK2 kinase activity and Rab10 substrate phosphorylation in a transient overexpression system and correlate this with in vivo patient data.

**Background:** In view of emerging targeted treatments and an increasing number of leucine-rich repeat kinase 2 (LRRK2) variants of uncertain clinical significance (VUS) identified by next-generation

sequencing in PD patients, there is a need for robust functional analysis of variant impact on LRRK2 kinase activity. LRRK2 is a large multidomain protein harbouring a tandem catalytic ROC-COR GTPase and kinase domains as well as an N-terminal armadillo, ankyrin and leucine-rich repeat and C-terminal WD-40 domains. All clearly pathogenic LRRK2 variants result in LRRK2 kinase activation with subsequent hyperphosphorylation of its endogenous substrates, a subgroup of RabGTPases including Rab10. Measuring LRRK2 dependent phosphorylation of Rab10 at Threonine 73 (pRab10Thr73) correlates with LRRK2 kinase activity.

**Method:** We use a transient overexpression system to evaluate LRRK2 variants in HEK293 cells in terms of their effect on LRRK2 kinase pathway activity using quantitative immunoblotting and targeted mass-spectrometry. We define LRRK2 variants as activating if they result in LRRK2 dependent Rab10 phosphorylation equal or above 1.5-fold compared to wildtype LRRK2. To correlate our cell-based overexpression assay with in vivo data, we have deployed our established peripheral blood neutrophil assay that requires fresh blood for measuring LRRK2 kinase activity in LRRK2 variant carriers compared to controls. To demonstrate that Rab10 phosphorylation at Threonine 73 is mediated by the LRRK2 kinase, peripheral blood neutrophils were treated ex vivo with and without the specific LRRK2 kinase inhibitor MLI-2.

**Results:** We have assessed over 200 variants that have previously been reported in patients in our HEK293 overexpression system and identified over 45 activating LRRK2 variants. Amongst them are all 7 well-established pathogenic variants as annotated in the MDSGene database ([www.mdsgene.org](http://www.mdsgene.org)). Activating variants tend to reside in the ROC, COR-B and kinase domains of LRRK2 and their effect size ranges from about 1.8-fold in the common G2019S, 4-fold in the R1441G and up to 6-fold in the Y1699C pathogenic LRRK2 variants. Our analysis also included 30 LRRK2 variants identified in non-PD patients with other movement disorders and none of them were activating. So far, we have been able to collect fresh peripheral blood neutrophils from carriers of 6 different LRRK2 mutations, VPS35 D620N and controls and demonstrate up to 8-fold increased LRRK2 dependent pRab10-Thr73 phosphorylation in the LRRK2 Y1699C variant compared to controls.

**Conclusion:** Our results provide a framework for functional LRRK2 variant interpretation in terms of kinase activation that may support the rationale for variant carrier inclusion or exclusion in ongoing or future LRRK2 targeting clinical trials and patient stratification in general. For any strongly activating LRRK2 variant as assessed in the HEK293 overexpression system (>3-fold increase in pRab10-Thr73 phosphorylation compared to LRRK2 wildtype), we predict that the effect can also be demonstrated in vivo in human peripheral blood neutrophils derived from carriers of these variants.

#### **LBA-4: Is plasma exosomal $\alpha$ -synuclein prognostic in Parkinson's disease (PD) patients? Role of niacin supplements.**

Wakae, C., Seamon, M., Hannah, Y., Giri, B., Morgan, J., Chong, R. (*Augusta, GA, USA*)

**Objective:** To determine that exosomal  $\alpha$ -synuclein in plasma is indicative of prognosis in PD and low-dose daily supplement of niacin is helpful.

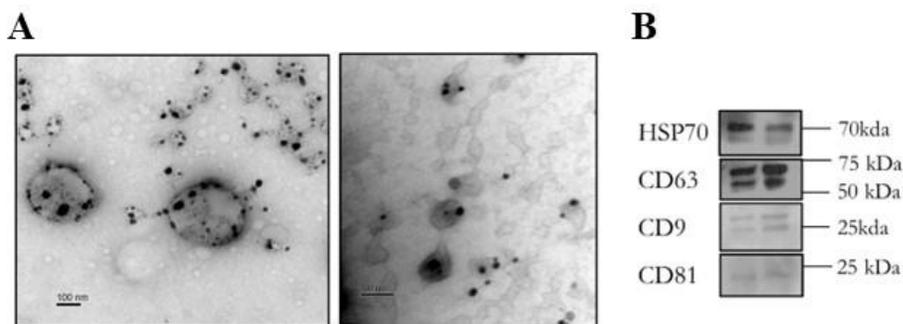
**Background:** We have demonstrated that daily niacin supplement in PD patients is beneficial to reduce UPDRS III scores. Niacin may act in multiple ways in a cell. Niacin is anti-inflammatory when it acts

through its receptor GPR109A or HCAR-2. Niacin increases NAD levels and thus boosts mitochondrial functions. We have demonstrated previously that phosphorylated  $\alpha$ -synuclein at serine residue 129 decreased in Parkinson's disease patients taking 250mg of daily niacin for six months while these levels in exosomes were increased in niacin group compared to the placebo group.

**Method:** The randomized trial of daily 250mg niacin or placebo lasted six months, with open-label niacin taken by both groups during the subsequent six months. Plasma samples and plasma exosomes were analyzed for  $\alpha$ -synuclein concentrations by electrochemiluminescence and enzyme-linked immunosorbent assays (ELISA) between April 2019 and May 2022.

**Results:** The level of  $\alpha$ -syn in exosomes was divided by the total plasma  $\alpha$ -syn level to find the ratio of plasma exosome to plasma concentration of each species of  $\alpha$ -syn. The total plasma exosome levels did not significantly differ between groups or time points. However, oligomers decreased from BL to 6MO in the placebo group by 1.7 ng/ml (95% CI, 0.2066 to 3.099; P=0.02). Significant changes were detected in the placebo group for the ratio of exosome to plasma p(s129)  $\alpha$ -syn and oligomers. The oligomer exosome to plasma ratio increased from 6 to 12MO during open-label niacin treatment (5.9 [95% CI, -11.3 to -0.5]; P=0.03). However, oligomers decreased from baseline (BL) to 6 months (6MO) in the placebo group by 1.6 ng/ml (95% CI, 0.1284 to 3.122; P=0.03). Additionally, L1 cell adhesion molecule (L1CAM) levels in plasma exosomes decreased in the placebo group from 6MO to 12MO by 0.14 ng/ml (95% CI, 0.028 to 0.25; P=0.014). When normalized to the concentration of exosomes, L1CAM levels showed a reduction between BL and 6MO in the niacin group by 0.006 (95% CI, 0.0002 to 0.012; P=0.041).

**Conclusion:** Reduced levels of aggregate forming  $\alpha$ -synuclein and modulated exosome-associated  $\alpha$ -synuclein in the periphery following niacin supplementation in PD indicates disease modification that may underlie the symptom improvements seen in previous trials.



**Figure 2: Isolation of exosomes using SEC**

- A) Image of plasma exosomes (left) and CSF (right) with CD9 gold label by TEM.
- B) Exosome markers shown by western.

**Explain how this abstract will be of broad significance and interest for MDS Members:**

Heterozygous GAA expansions in FGF14 have been recently shown to cause the dominantly inherited cerebellar ataxia (CA) SCA27B. Whether it represents a common genetic cause of sporadic late onset cerebellar ataxia (SLOCA) remains undetermined.

In this work we utilized a cohort of undiagnosed SLOCA patients prospectively followed in the neurology department of Strasbourg University Hospital to (1) determine the prevalence of GAA-FGF14-CA in a European cohort, (2) isolate discriminative features and (3) map disease progression using prospectively collected quantitative longitudinal data.

We screened FGF14 GAA expansion among 118 undiagnosed SLOCA patients. Prevalence of GAA-FGF14-CA was 12.7%. Higher age-of-onset, higher Spinocerebellar Degeneration Functional Score, presence of vertigo, diplopia, nystagmus, sensori-motor neuropathy and absence of dysautonomia including orthostatic hypotension at baseline were significantly associated with SCA27B diagnosis. Ataxia progression was  $\approx 0.4$  Scale for the Assessment and Rating of Ataxia (SARA) point per year. To detect a 50% reduction in SARA score progression with 80% power a total of 1357 patients would be required in a 2-year parallel-groups trial.

This manuscript has important practical consequences as it suggests that heterozygous FGF14 GAA expansions are by far the most common genetic cause of SLOCA and should be systematically searched for facing patients presenting with this phenotype. The low progression rate on SARA score foretell future challenges for the upcoming neuroprotection trials and highlight the need for surrogate outcome markers including blood or imaging biomarkers.

#### **LBA-5: Natural history and phenotypic spectrum of GAA-FGF14 sporadic late-onset cerebellar ataxia (SCA27B)**

Wirth, T., Clément, G., Delvallée, C., Bonnet, C., Bogdan, T., Iosif, A., Schalk, A., Chanson, J-B., Pellerin, D., Brais, B., Roth, V., Wandzel, M., Fleury, M-C., Piton, A., Calmels, EN., Namer, I., Kremer, S., Tranchant, C., Renaud, M., Anheim, M. (*Strasbourg, France*)

**Objective:** To estimate the prevalence, characterize the phenotypic spectrum, identify discriminative features, and model longitudinal progression of SCA27B in a prospective cohort of sporadic late-onset cerebellar ataxia (SLOCA) patients.

**Background:** Heterozygous GAA expansions in FGF14 gene have been related to autosomal dominant cerebellar ataxia (SCA27B-MIM:620174). Whether it represents a common cause of SLOCA remains to be established.

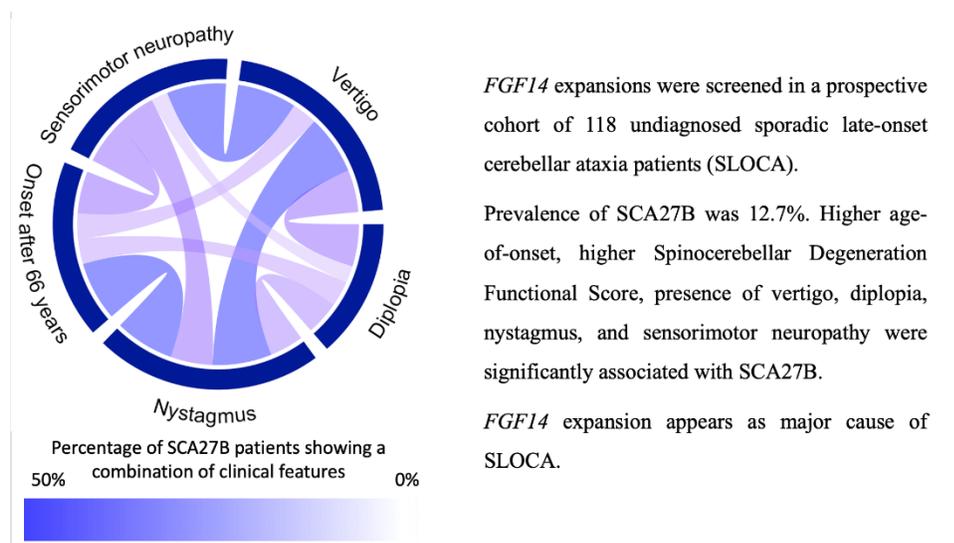
**Method:** FGF14 expansions screening combined with longitudinal deep-phenotyping in a prospective cohort of 118 SLOCA patients (onset >40 years-of-age, no family history of cerebellar ataxia) without definite diagnosis.

**Results:** Prevalence of SCA27B was 12.7% (15/118). Higher age-of-onset, higher Spinocerebellar Degeneration Functional Score, presence of vertigo, oculomotor disorders, diplopia, nystagmus, sensorimotor neuropathy and absence of dysautonomia including orthostatic hypotension were

significantly associated at baseline with SCA27B. Ataxia progression was  $\approx 0.4$  point per year on Scale for Assessment and Rating of Ataxia. To detect a 50% reduction in SARA score progression with 80% power a total of 1357 patients would be required in a 2-year parallel-groups trial

Conclusion: In conclusion, we demonstrated that heterozygous FGF14 GAA expansion is a major cause of SLOCA, with significant upcoming challenges in trial design for the identification of therapeutic agents. Further prospective works aiming to longitudinally investigate clinical progression and identify imaging or blood sample biomarkers are warranted.

T.W. received honoraria from IPSEN, Abbvie, Edimark, research grants from the Revue Neurologique, the Fondation Planiol and the APTES organizations, prize from the Société Fra



#### **LBA-6: Cholinergic System Upregulation Associated with Cognitive Stability in Parkinson's Disease**

Carli, G., van der Zee, S., Slomp, A., Kanel, P., Slingerland, S., Kovacs, R., Boertien, J., Albin, R., Bohnen, N., van Laar, T. (*Ann Arbor, MI, USA*)

Objective: To investigate longitudinal cholinergic system changes in Parkinson's disease (PD) with and without cognitive decline.

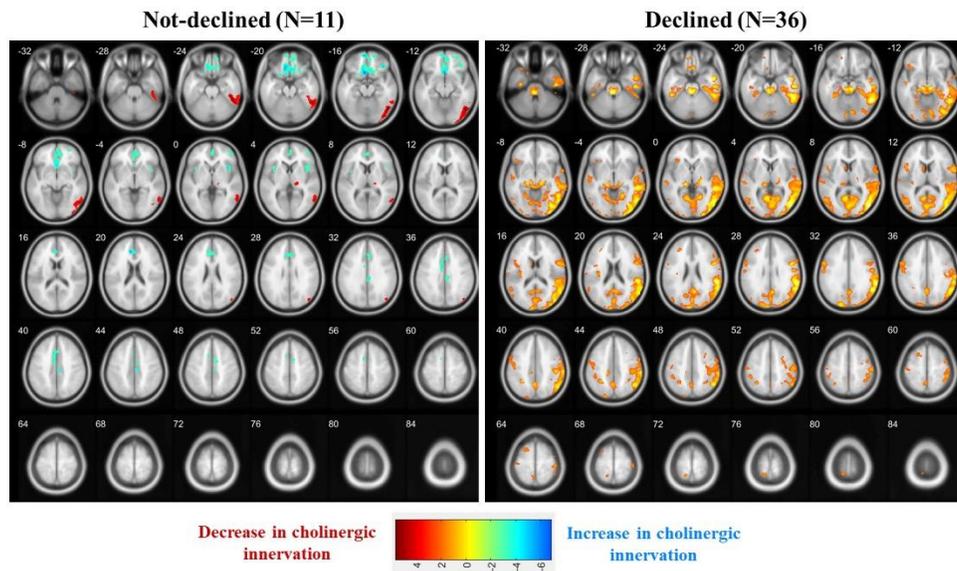
Background: Incomplete characterization of central cholinergic systems changes during disease progression in vivo hinders understanding of the contributions of cholinergic systems degeneration to cognitive decline in PD. Investigating the kinetics of cholinergic systems changes and associations with cognitive decline might identify useful biomarkers and novel therapeutic targets.

Method: A prospective cohort study (DUPARC) recruited 150 de novo PD subjects in the northern Netherlands. Follow-up assessments were conducted every 3 years, including cognitive function evaluations and 18F-FEOBV PET scans to measure regional cholinergic terminal density. Forty-seven subjects completed the initial 3-year follow-up. Cognitive trajectories were determined based on a decline threshold of  $>1$  SD on neuropsychological tests. Based on this threshold, two groups were

identified: PD patients without cognitive decline (no tests of >1 SD decline) and patients with cognitive decline (1 or more tests with >1 SD decline). Changes in 18F-FE0BV binding were analyzed in each group using voxel-wise repeated measures ANOVA in SPM12, correcting for age. Statistical significance was set at p50 voxels.

Results: PD subjects without cognitive decline (N=11) at three years demonstrated increased 18F-FE0BV binding in the anterior and middle cingulate cortex, middle and superior orbitofrontal gyrus, and bilateral insula. The same subjects showed declining 18F-FE0BV binding limited to the right middle and inferior temporal gyrus. PD patients with cognitive decline (N=36) exhibited declining 18F-FE0BV binding in the midbrain, occipital-parietal, and temporal regions with no significant increase of 18F-FE0BV binding.

Conclusion: This study presents in vivo evidence linking regional cholinergic terminal density changes to cognitive decline in PD. Our findings suggest that PD subjects without cognitive decline exhibit upregulation of cholinergic neurotransmission in the anterior cingulate and orbitofrontal cortex. This upregulation may serve as a compensatory mechanism to maintain or enhance acetylcholine neurotransmission despite underlying cholinergic dysfunction, perhaps mitigating the cognitive decline in PD.



### **LBA-7: Multiplex proteomic identifies fluid biomarkers for phenoconversion in prodromal and early Parkinson's Disease**

Bartl, M., Dakna, M., Schade, S., Marek, K., Siderowf, A., Foroud, T., Hutten, S., Frasier, M., Casey, B., Muntean, M-L., Sixel-Döring, F., Trenkwalder, C., Mollenhauer, B. (*Göttingen, Germany*)

**Objective:** To evaluate biomarkers in plasma from established cohorts of prodromal synuclein aggregation disorders, including Parkinson's disease (PD). To identify progression to disease and elucidate the pathophysiology of phenoconversion.

**Background:** Assessing subjects at risk towards the development of disease for identifying biomarkers is an unmet need to support potential neuroprotective therapies in clinical trials.

**Method:** Proximity Extension Assay (PEA) technology with the OLINK® 1536 panel was applied in longitudinal plasma samples of subjects from three different longitudinal cohorts: Parkinson Associated Risk Study (PARS, 78 subjects with hyposmia, follow-up 10 years), de novo Parkinson's cohort [DeNoPa, 48 subjects with isolated REM Sleep Behaviour Disorder (iRBD), follow-up 8 years] and Parkinson Progression Marker Initiative cohort (PPMI, 67 subjects with hyposmia, iRBD), follow-up 7 years). Overall, 37 subjects converted. Additional 44 subjects with very short duration of PD from PPMI were added on as proxy converters to increase statistical power. Hence a total of 81 PD subjects were thus compared to 156 that did not develop the disease during follow-up. We used linear mixed models to analyze the longitudinal changes and predictive potential of these markers in regard of conversion to disease.

**Results:** Analysis of converter vs. non-converter revealed 63 proteins that changed longitudinally, including the increase of several markers of inflammatory pathways in converters, like Interleukin(IL)-15, CD200 and the corresponding receptors to IL-5, IL 17A and IL-1R1. Further, proteins of dopaminergic cell development/maintenance showed alterations like increased DOPA decarboxylase, and decreased Cysteine-rich motor neuron 1 protein and the Wnt-signaling molecule Secreted frizzled-related protein 1. Markers of cardiovascular functioning showed evidence for increased neovascularization including Endothelial cell-specific molecule 1. These proteins already showed different BL levels, revealing a potential to predict conversion.

**Conclusion:** Multiplex PEA enabled the molecular assessment of conversion from prodromal stages to clinically manifest disease that include pronounced inflammatory activity in the periphery, regenerative vascular processes, and neuronal dysfunction. With further validation, these findings will enable biomarker development for clinical trials and help to understand the development to disease for upcoming prevention trials.

### **LBA-8: A CNN-based Approach to Classification of Parkinson's Disease Patients with and without Freezing of Gait during 360° Turning Task**

Cheon, S., Kim, JW. (*Busan, Korea*)

**Objective:** To verify the modeling approach using visual images for identification of gait freezing in Parkinson's disease.

**Background:** Parkinson's disease (PD) is one of the neurodegenerative diseases, and the cause is still unclear, so it is difficult to diagnose early, subjective diagnosis of severity according to degeneration of motor symptoms and disease progression, and objective and quantitative indicators for disease progression evaluation are insufficient. A classification modeling approach using visual images (Convolutional Neural Network, CNN algorithm) converted from time-series gait data will improve the accuracy of disease severity discrimination.

**Method:** The subjects of this study were each 30 PD patients with and without freezing of gait (freezers and non-freezers) and 30 healthy control group (controls) of the same age. PD patients performed the 360° turning tasks in the direction of the more affected side at the preferred speed in an off state of medication. Position and acceleration data of 40 body segments marker trajectories, including the center of mass, were used to analyze the time-series data of the turning phase. These position and acceleration time-series data were converted into new imaging and trained with a CNN algorithm technique. The performance of the three-group classification model was evaluated using accuracy.

**Results:** The body segments with the highest performance in classifying freezers, non-freezers, and controls were the left elbow at 61%, right tibia at 60%, and right ankle at 60% in the image-based position time-series data when using the Recurrence Plot (Rec) algorithm and were the left upper arm at 60% and left knee at 60% when using the Gramian Angular Summation Field (GASF) algorithm. In addition, the left toe at 62% and right toe at 58% were found in the image-based acceleration time-series data when using the Rec algorithm. These results showed that freezers observed uncoordinated gait patterns between the left elbow and knee with more affected body segments and asymmetric steps to complete turning compared to non-freezers and controls. Therefore, freezers may have trouble performing automatized movements without attention during turning.

**Conclusion:** The time-series gait pattern was confirmed using the whole-body segments during 360° turning tasks on the affected side at the preferred speed in freezers and non-freezers. In addition, the CNN technique based on time-series gait data imaging may improve the availability as an objective indicator of disease severity in a clinical environment through early diagnosis of motor symptoms such as freezing of gait in PD patients.

#### **LBA-9: Opicapone as adjunctive to levodopa-treated Parkinson's disease patients without motor complications: preliminary data from the EPSILON Study**

Ferreira, JJ, Rascol, O., Stocchi, F., Antonini, A., Moreira, J., Castilla-Fernández, G., Rocha, J.F., Holenz, J., Poewe, W. (Lisbon, Portugal)

**Objective:** This study aimed to explore the potential of opicapone (OPC) to enhance the clinical benefit of levodopa (L-DOPA)/dopa decarboxylase inhibitor (DDCi) in patients with Parkinson's disease (PD) without motor complications.

**Background:** Opicapone (OPC) has proven to be generally well-tolerated and efficacious in reducing OFF-time in L-DOPA/DDCi treated patients with Parkinson's disease (PD) and end-of-dose motor fluctuations.

**Method:** This was a double-blind, multicenter, randomized, placebo-controlled study. Three-hundred and fifty-five (355) PD patients were randomly assigned (1:1) to OPC-50mg once-daily or placebo. A 4-week screening-period was followed by a 24-week maintenance phase. The primary efficacy endpoint was the change from baseline to week-24 in MDS\_UPDRS-III. Secondary endpoints included tolerability, clinical global impression of improvement (CGI-I, both patient and clinician) and MDS\_UPDRS-IV.

**Results:** At week-24, the mean(SE) change from baseline in MDS\_UPDRS-III score for the OPC-50mg arm was -6.5(0.7) versus -4.3(0.7) for the placebo arm resulting in a significant difference of -2.2(0.9) favouring OPC-50mg (p-value=0.010). A significantly higher proportion of OPC-treated patients reported an improvement in their clinical condition (58% vs 46% in placebo, as assessed by patient PGI-I). A similar trend, but not significant, was observed for the CGI-I (50% vs 46% in placebo). Fewer OPC-50mg treated patients (5.5% vs 9.8% in placebo) reported motor complications in MDS\_UPDRS-IV (0.3 points vs 0.4 in placebo). The frequency and types of adverse events reported were similar between OPC-treated and placebo-treated patients.

**Conclusion:** The addition of adjunct opicapone in levodopa-treated PD patients without motor complications significantly improved motor function.

#### **LBA-10: Chronic administration of GV1001 improved motor and cognitive function and ameliorated tau aggregates in TauP301L-BiFC Mouse (4R-tau model): implication to a phase 2 clinical trial for PSP in Korea**

Lee, J-Y., Kim, Y., Lim, S., Kang, D., Cho, H. (*Seoul, Korea*)

**Objective:** This investigation evaluates the effect of GV1001 on impaired motor and cognitive functions in TauP301L-BiFC mouse, a novel 4R-tau animal model generated to monitor tau self-assembly in the brain.

**Background:** Progressive supranuclear palsy (PSP), a 4R tauopathy, is a rapidly progressive atypical parkinsonian syndrome with severe disabilities in motor and cognitive functions. Until now there have been no therapeutics successfully developed for PSP. GV1001, a 16 amino acid peptide corresponding to a fragment of the catalytic site of telomerase, has shown various extra-telomeric functions such as anti-inflammation, anti-oxidative stress, and neuroprotective effects (1-4).

**Method:** To monitor and quantify human tau self-assembly in the brain, bimolecular fluorescence complementation (BiFC) technology was applied to tau (2N4R) containing P301L mutation. By using the TauP301L-BiFC mouse model, the efficacy of GV1001 in 4R tauopathy was evaluated. GV1001 was subcutaneously injected into TauP301L-BiFC mice three times per week for 21 weeks and LMTM, a tau protein aggregation inhibitor, was administered as a reference drug.

**Results:** Groups injected with GV1001 (1 and 2 mg/kg) showed significantly improved motor and cognitive functions compared with controls. Histological exam showed that GV1001 inhibited 4R tau aggregation in the somatosensory/motor cortex, hippocampus Cornus Ammonis-1 (CA1), and substantia nigra of TauP301L-BiFC mouse. Furthermore, the level of 4R tau phosphorylation at S202/T205 sites in the brain was decreased in groups treated with GV1001.

Conclusion: Present data show that GV1001 improves motor and recognition deficits by inhibiting the hyper-phosphorylation and aggregation of human 4R tau in TauP301L-BiFC, a novel mouse model for PSP. Based on the experiments, a phase-2a double-blind randomized placebo-controlled trial of GV1001 in PSP patients has been launched in South Korea. A total of 75 patients are going to be randomized to placebo, 0.56 mg, and 1.12 mg groups in 5 centers and to get subcutaneous injections of the investigational drug every 2 weeks for 6 months. This trial is aimed to investigate the feasibility and safety of GV1001 as a potential therapeutic drug in PSP, and patient recruitment is expected to be completed in the first term of 2024.

References: Neuroprotective Effects of GV1001 in Animal Stroke Model and Neural Cells Subject to Oxygen-Glucose Deprivation/Reperfusion Injury. Kwon HS, Kim YE, Park HH, Son JW, Choi H, Lee YJ, Kim HY, Lee KY, Koh SH. *J Stroke*. 2021 Sep;23(3):420-436.

### **LBA-11: Effect of $\beta$ -amyloid deposition on regional cerebral cholinergic vesicular transporter binding in Parkinson's disease: a dual-ligand [18F]-FEOBV and [11C] PIB PET study**

Kanel, P., Roytman, S., Brown, T., Frey, K., Scott, P., Koeppe, R., Albin, R., Bohnen, N. (*Ann Arbor, MI, USA*)

Objective: To investigate possible cholinergic vulnerability associated with  $\beta$ -amyloid plaques in persons with Parkinson's disease (PD).

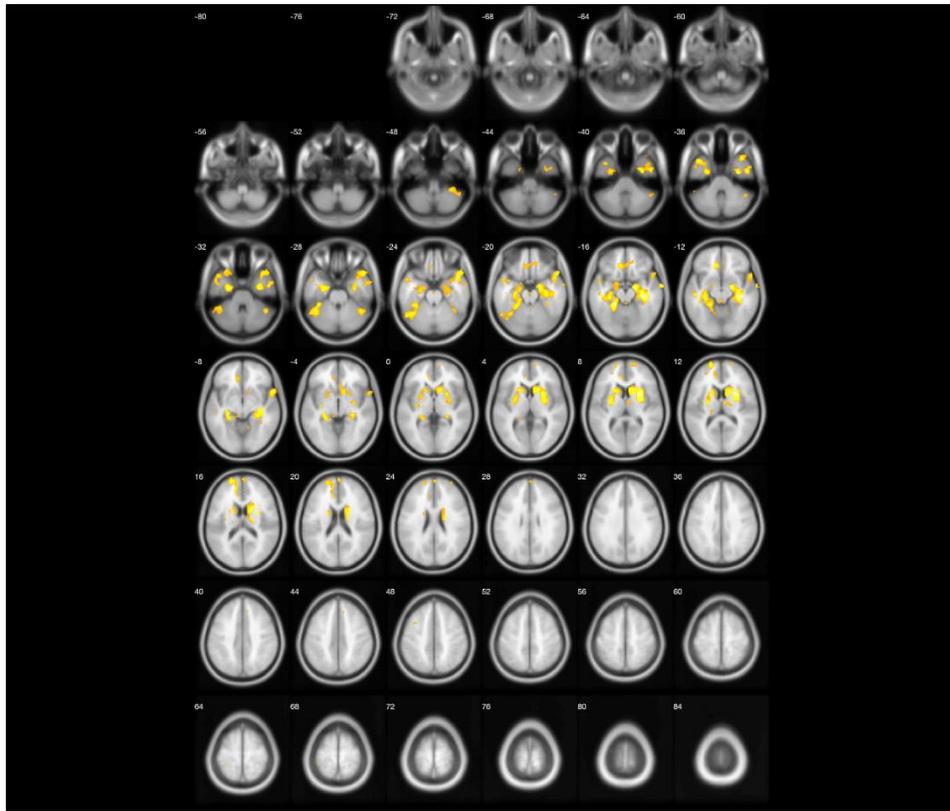
Background:  $\beta$ -amyloid plaque deposition is key pathobiological hallmark of Alzheimer's disease. There is also evidence of cognitive detrimental effects of  $\beta$ -amyloid deposition in Parkinson's disease (PD), even at low levels. Here, we investigate whether  $\beta$ -amyloid burden is associated with cholinergic deficits in specific brain regions in individuals with PD.

Method: 64 PD subjects (53 males, 11 females; age:  $68.6 \pm 8.19$ ; disease duration:  $6.60 \pm 4.59$ ; HY:  $2.61 \pm 0.61$ ; MDS-UPDRS-III motor scores:  $37.52 \pm 13.09$ ; MOCA:  $25.97 \pm 3.14$ ) underwent vesicular acetylcholine transporter (VAcHT) [18F]-fluoroethoxybenzovesamicol (FEOBV) PET, [11C]-Pittsburgh compound B  $\beta$ -amyloid PET, and MR imaging. Distribution volumes ratio (DVR) were computed using Logan plot analysis for [11C]-PIB with cerebellar reference regions. The parametric imaging for [18F]-FEOBV was created by using supratentorial white matter as a reference region. We performed SPM12 whole brain voxel-based VAcHT PET group comparison analysis between  $\beta$ -amyloid-positive ( $A\beta+$ ) (DVR > 1.10) PD subjects and  $\beta$ -amyloid-negative ( $A\beta-$ ).

Results: SPM12 analysis showed regional VAcHT binding reductions (figure 1) in striatum, hippocampus, amygdala, anterior cingulum, mesofrontal structures, paralimbic structures, lateral geniculate nucleus, and cerebellum in  $A\beta+$  (n=17) compared to  $A\beta-$  PD participants (n=47).

Conclusion: There is evidence of a specific topography of regional cerebral cholinergic vulnerability in striatal, metathalamic, limbic, limbocortical and paralimbic structures that all play important roles in cognition. The pattern of selective cholinergic vulnerability is different from typical areas of  $\beta$ -amyloid plaque deposition.  $\beta$ -amyloidopathy may exert a synergistic detrimental influence on cholinergic nerve terminals in key cognitive regions in PD.

Acknowledgement or Disclosure: This work was supported by the Department of Veterans Affairs (I01 RX001631); the Michael J. Fox Foundation; and the National Institutes of Health (grant numbers P01 NS015655, P50 NS091856, R01 NS099535, RO1 NS070856, P50 NS123067, and R01 AG073100).



**LBA-12: Safety and tolerability of UCB0022, a dopamine 1 (D1) receptor modulator in people with Parkinson’s (PwP) and healthy participants: first results of a Phase 1 study**

Biagioni, M. C., Qamar, M., Yamamoto, T., Benoit, A., Clarke, B., Lelij, G., Nicholl, R., Boyce, M., Hervé, C., Vroye, L., Ray Chaudhuri, K., Famodimu, O., (*Braine-l’Alleud, Belgium*)

Objective: To assess safety and tolerability of UCB0022, a novel small molecule D1 positive allosteric modulator (D1PAM), when administered in single-ascending and multiple-ascending doses, with and without titration, to healthy participants and as a repeat dose with titration in people with Parkinson’s (PwP).

Background: Novel allosteric modulation of D1 receptors may provide a useful clinical strategy to combat chronic levodopa induced motor fluctuations in PwP. UCB0022 is an orally available, brain-penetrant small molecule D1PAM, which in preclinical studies shows potency and selectivity, is devoid of intrinsic activity and increases D1 signalling 10-fold in the presence of dopamine.

**Method:** This was a randomised, participant-blind, investigator-blind, placebo-controlled, first-in-human study of once-daily oral UCB0022 or placebo in healthy participants and PwP (NCT04867642). The primary outcome measure was incidence of treatment-emergent adverse events (TEAEs).

**Results:** We report preliminary safety and tolerability data from three parts of the study: Part A, a single ascending dose in two alternating cohorts of healthy participants (N=31; mean age 36.7 years [range 19–55 years]); Part B, multiple ascending doses and a repeat dose with titration with a parallel design in healthy participants (N=48; mean age 33.6 years [range 18–54 years]); Part C, a repeat dose with titration in people with mild-to-moderate Parkinson's (N=12; mean age 60.1 years [range 43–74 years]; Hoehn and Yahr stages 1 to 3 inclusive). All reported TEAEs were mild or moderate. Transient, dose-related changes in vital signs were observed; however, no study participant reached study prespecified values of 'potentially clinically meaningful' blood pressure increase (>160/100mmHg). The incidence of TEAEs and cardiovascular responses were lower in cohorts with titration compared with cohorts that received the same dose without titration.

**Conclusion:** UCB0022 demonstrated an acceptable safety and tolerability profile in healthy participants and PwP. No new safety concerns were identified; there were no deaths, serious TEAEs or TEAEs of severe intensity reported in any part of the study. Titration reduced the incidence and severity of TEAEs and showed fewer effects on vital signs. Based on these results, UCB0022 will progress to Phase 2.

**Acknowledgement or Disclosure:** This study was funded by UCB Pharma

**LBA-13: Neuroprotective effect of GT-02287, a brain-penetrant structurally targeted allosteric regulator of glucocerebrosidase, leads to a significant reduction of plasma NfL levels and improvement in behavioural deficits in a mouse model of GBA1 Parkinson's disease**

Calvo-Flores Guzman, B., Perez, N., Garcia-Collazo, A., Cubero, E., Barril, X., Bellotto, M., Taylor, J.,  
(Ticino, Switzerland)

**Objective:** To investigate the effect of GT-02287 on neuropathological, motor and biomarker readouts in a mouse GBA1-PD model.

**Background:** Mutations in the GBA1 gene encoding lysosomal enzyme glucocerebrosidase (GCase) represent the most significant genetic risk factor for Parkinson's disease (PD). Misfolded and dysfunctional GCase expressed by mutated GBA1 are linked to impaired lysosomal function and  $\alpha$ -synuclein accumulation. CBE, a covalent inhibitor of GCase, can induce a partial deficit in GCase activity comparable to that associated with GBA1-PD. Gain Therapeutics applied its proprietary computational drug discovery platform, SEE-Tx<sup>®</sup>, to discover small molecule allosteric GCase modulator, GT-02287. GT-02287 stabilizes misfolded GCase, protects it from degradation, facilitates its trafficking to the lysosome and restores its function. Neurofilament light chain (NfL) is an emerging neurodegeneration biomarker that recently has been successfully used as a surrogate endpoint for accelerated approval in ALS and exploratory endpoint in neuronopathic MPS II clinical trials.

**Method:** Mice were treated with CBE (100 mg/kg, i.p.) and GT-02287 (30, 60, 90 or 120 mg/kg p.o.) q.d. for 14 days. Aggregated  $\alpha$ -synuclein, Iba-1, tyrosine hydroxylase (TH) and NeuN were assessed by immunostaining and confocal microscopy. Striatal dopamine level was assessed by LC-MS/MS. Plasma

NfL levels were assessed by ELISA. Behavioural deficits were assessed by the wire hang and beam walk tests.

Results: GT-02287 reduced aggregated  $\alpha$ -synuclein, neuroinflammation, neuronal death and plasma NfL levels, as well as increasing striatal dopamine levels and motor function in CBE-injured mice.

Conclusion: Augmentation of GCase function by GT-02287 protects against key pathophysiological hallmarks of PD and provides a neuroprotective effect reflected by a significant reduction in plasmatic levels of NfL, a marker for neurodegeneration, as well as improving motor deficits. GT-02287 emerges as a potential disease-modifying, orally bioavailable therapy for PD.

#### **LBA-14: Phenotypic spectrum of GAA-FGF14 ataxia (SCA27B) patients: an Italian multicenter cohort study**

Satolli, S., Petrucci, A., Bruno, G., Capacci, E., Casali, C., Ceravolo, R., De Micco, R., De Michele, G., Ferrari, C., Filla, A., Fini, N., Govoni, A., Lopergolo, D., Malandrini, A., Mignarri, A., Musumeci, O., Pellicchia, M.T., Perna, A., Ravenni, R., Ricca, I., Rossi, S., Rufa, A., Silvestri, G., Tessitore, Pellerin, D., Brais, B., Santorelli, F.M. (Pisa, Italy)

Objective: We aimed to characterize the clinical phenotype of Italian patients affected by autosomal dominant spinocerebellar ataxia due to intronic GAA repeat expansion (RE) in the FGF14 gene (GAA-FGF14 ataxia; SCA27B) collected in a multicenter study.

Background: Genetic diagnosis of adult onset ataxia is often difficult and elusive. GAA-FGF14 ataxia/SCA27B is a recently identified, relatively common, potentially treatable form of late onset ataxia.

Method: We analyzed the clinical, genetic and neuroradiological features of 25 index cases carrying a heterozygous GAA-FGF14 RE. We also focused on 4-aminopyridine (4-AP) treatment response.

Longitudinal clinical records were systematically assessed according to a comprehensive eCRF data form. We assessed disease severity and progression by using the Scale for the Assessment and Rating of Ataxia (SARA), the Friedreich Ataxia Rating Scale functional disability stage (FARS-DS) and functional impairment in terms of mobility aids. Finally, we analyzed longitudinal SARA scores by linear regression over disease duration.

Results: Seventeen out of 25 GAA-FGF14 patients consistently presented as late-onset (57.5 years  $\pm$  14.4) cerebellar syndrome, partly combined with afferent sensory deficits (30%). A single case, age 17 years, was asymptomatic at the time of our study, though his examination was significant for mild intellectual disability and slight pyramidal signs in lower limbs. All symptomatic individuals showed evidence of impaired balance and gait; cerebellar oculomotor signs (saccadic intrusion, nystagmus, slowing saccades) were also frequent (78%). Episodic manifestations at onset occurred in 39% of patients; episodes were characterized mostly by dysarthria (44%) and vertigo (55%). Dysautonomia and cognitive impairment were infrequent. Peripheral neuropathy was reported in 26% of patients. Brain magnetic resonance imaging showed cerebellar atrophy in most cases (18/21). Longitudinal assessments indicated slow progression of ataxia (0.33 SARA points/year) and minimal functional impairment (11 patients are still fully ambulant after 8 years of disease duration). We found no correlation between RE, age at onset, longitudinal SARA scores or disease duration. Series of N-of-1 trials with 4-AP are ongoing.

Conclusion: Consistent with previous reports, Italian GAA-FGF14 patients present an adult-onset, slowly progressive cerebellar ataxia with predominant impairment of balance and gait and frequent cerebellar oculomotor signs.

Combined with multisite international efforts, our study paves the way towards large-scale natural history studies in this newly discovered late-onset ataxia.

### **LBA-15: Short-latency DBS-evoked cortical potentials are related to stimulation of the hyperdirect pathway**

Dembek, T., Peeters, J., Boogers, A., Van bogaert, T., Gransier, R., Wouters, J., De Vloo, P., Nuttin, B., Barbe, M., Mc Laughlin, M. (*Cologne, Germany*)

Objective: To investigate the neuroanatomical origin of deep brain stimulation (DBS) evoked cortical potentials by combining EEG-recordings with structural connectivity analyses.

Background: DBS evoked cortical potentials (ECPs) – especially those with short latencies around 3 ms – might serve as biomarkers for DBS settings with beneficial motor effects in subthalamic nucleus (STN) DBS for Parkinson's disease (PD). Retrograde activation of the hyperdirect pathway (HDP) has been suggested as the origin of short latency ECPs.

Method: ECPs were recorded with 64 channel-EEG during 10 Hz STN-DBS from different stimulation contacts in 13 PD patients (18 hemispheres; 180 contacts). Fiber-wise stimulation mapping was performed using a structural connectome based on the PPMI dataset. Fiber wise weighted linear regression was used to identify fibers significantly associated with both short latency (3ms) and long-latency (10ms) ECPs. Leave-one-patient-out crossvalidation determined whether stimulation overlap with significant fibers predicted ECP amplitudes.

Results: Fibers associated with short-latency ECPs traversed in accordance with current anatomical models of the HDP linking the premotor cortices to the posterodorsal STN and then continuing towards more medial regions like the zona incerta (see figure 1). Fibers associated with long-latency ECPs traversed more ventrally within the substantia nigra. Overlap with significant fibers for short/long-latency ECPs significantly and specifically predicted the respective ECP amplitude during crossvalidation

Conclusion: Our results provide evidence that short latency ECPs indeed are associated to stimulation of the HDP while long-latency ECPs are associated with stimulation of neighboring neuroanatomical structures, especially the substantia nigra. Short-latency ECPs can thus serve as a potential biomarker for STN-DBS in PD.

Acknowledgement or Disclosure: Till Anselm Dembek was supported by the Cologne Clinician Scientist Program (CCSP)/ Faculty of Medicine/ University of Cologne, funded by the German Research Foundation (DFG, FI 773/15-1).

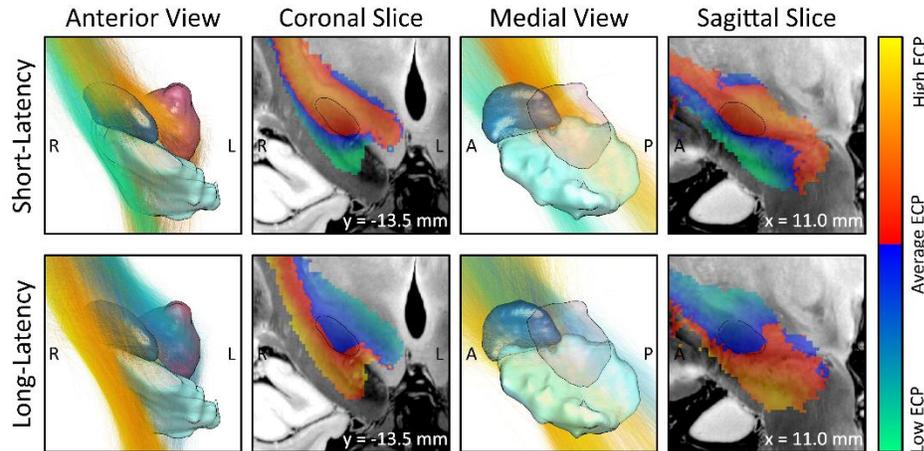


Figure 1: Fiber-wise mapping of short-latency (upper row) and long-latency (lower row) ECPs. In the 3D renderings, only significant fibers are shown. Red to yellow indicates fibers significantly associated with higher than average ECP amplitudes while blue to green highlights fibers significantly associated with lower than average ECP amplitudes. Neuroanatomical structures: STN – blue; Substantia nigra – mint; Red nucleus – magenta.

### **LBA-16: Dystonia due to ANO3 variants cause abnormal Ca<sup>2+</sup> signalling, K<sup>+</sup> channel activity, and cell death**

Ortigoza Escobar, JD., Ousingsawat, J., Talbi, K., Gómez-Martín, H., Koy, A., Fernández-Jaén, A., Tekgül, H., Serdaroğlu, E., Schreiber, R., Kunzelmann, K. (*Barcelona, Spain*)

**Objective:** The main aim of this study was to comprehensively evaluate the clinical, radiological, and molecular characteristics of individuals with ANO3 variants. By investigating the effects of ANO3 variants on intracellular calcium signaling and ion channel activation, the study sought to elucidate the pathophysiology underlying this disorder. Additionally, the study aimed to identify novel ANO3 variants and establish a link between these variants and the specific dystonic phenotype observed in the patients.

**Background:** Anoctamin 3 (ANO3) belongs to a family of transmembrane proteins that form phospholipid scramblases and ion channels. A large number of ANO3 variants were identified as the cause of craniocervical dystonia, but pathogenic mechanisms remain obscure. It was suggested that ANO3 variants may dysregulate intracellular Ca<sup>2+</sup> signalling, as variants in other Ca<sup>2+</sup> regulating proteins like hippocalcin were also identified as a cause of dystonia.

**Method:** Four children with heterozygous ANO3 variants from four independent families were identified through international collaborations. Comprehensive clinical, genetic, radiological, and biochemical data were collected, and various assessments were performed. Genetic analysis was conducted using whole exome sequencing and targeted Sanger sequencing methods. Cell culture experiments were performed using skin fibroblasts and HEK293T cells. Molecular techniques such as RT-PCR and cloning were used to study ANO3 variants. Immunocytochemistry and Western blotting were employed for protein visualization. Intracellular calcium measurements and patch clamping were conducted to assess cellular function. Flow cytometry and LDH and PI assays were used to analyze cell death. Statistical analysis was performed to determine significant differences.

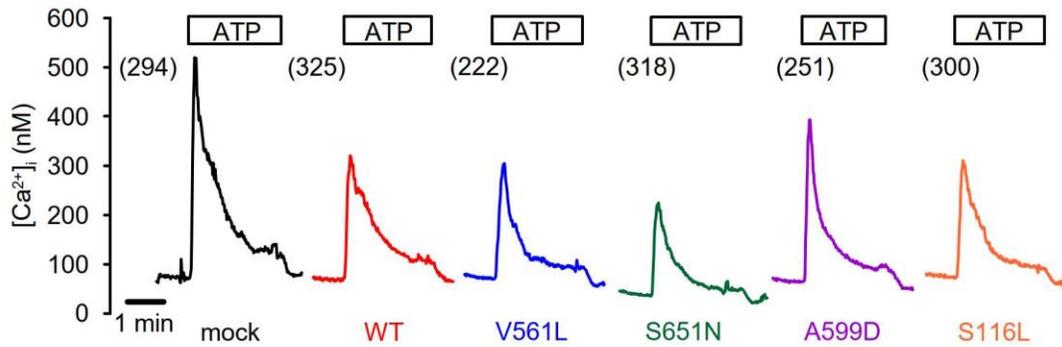
Results: The median age at follow-up was 6.6 years (ranging from 3.8 to 8.7 years). The majority of individuals presented with hypotonia and motor developmental delay. Two patients exhibited generalized progressive dystonia, while one patient presented with paroxysmal dystonia. Additionally, another patient exhibited early dyskinetic encephalopathy. One patient underwent bipallidal deep brain stimulation (DBS) and showed a mild but noteworthy response, while another patient is currently being considered for DBS treatment. Neuroimaging analysis of brain MRI studies did not reveal any specific abnormalities (Table 1). The molecular spectrum included two novel ANO3 variants (V561L and S116L) and two previously reported ANO3 variants (A599N and S651N).

As anoctamins are known to affect intracellular Ca<sup>2+</sup> signals, we compared Ca<sup>2+</sup> signalling and activation of ion channels in cells expressing wild type ANO3 and cells expressing ANO variants. Novel V561L and S116L variants were compared with previously reported A599N and S651N variants and with wtANO3 expressed in fibroblasts isolated from patients, or when overexpressed in HEK293 cells (Figure 1). We identified ANO3 as a Ca<sup>2+</sup>-activated phospholipid scramblase that also conducts ions. Impaired Ca<sup>2+</sup> signalling and compromised activation of Ca<sup>2+</sup> dependent K<sup>+</sup> channels were detected in cells expressing ANO3 variants. In the brain striatal cells of affected patients, impaired activation of KCa3.1 channels due to compromised Ca<sup>2+</sup> signals may lead to depolarized membrane voltage and neuronal hyperexcitability and may also lead to reduced cellular viability, as shown in the present study.

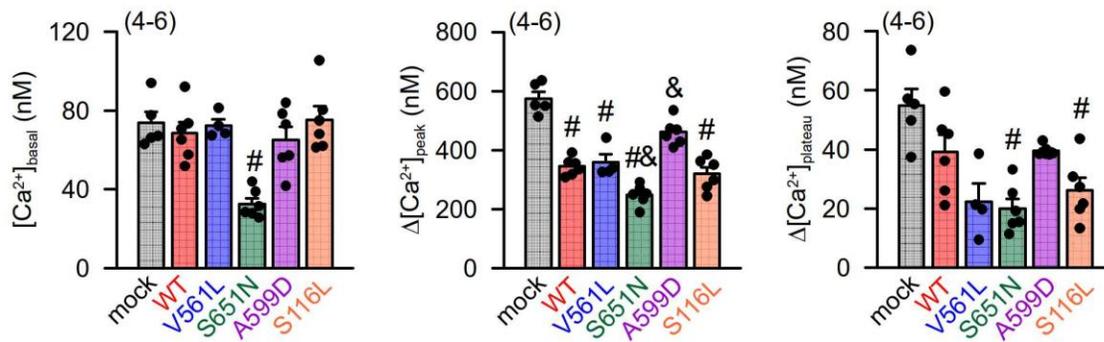
Conclusion: In conclusion, our study reveals the association between ANO3 variants and paroxysmal dystonia, representing the first reported link between these variants and this specific dystonic phenotype. We demonstrate that ANO3 functions as a Ca<sup>2+</sup>-activated phospholipid scramblase and ion channel: cells expressing ANO3 variants exhibit impaired Ca<sup>2+</sup> signalling and compromised activation of Ca<sup>2+</sup>-dependent K<sup>+</sup> channels. These findings provide a mechanism for the observed clinical manifestations and highlight the importance of ANO3 for neuronal excitability and cellular viability.

Acknowledgement or Disclosure: The authors thank all participants and their families for their support. We are indebted to the “Biobanc de l’Hospital Infantil Sant Joan de Déu per a la Investigació” integrated in the Spanish Biobank Network of ISCIII for the sample and data procurement

A



B



### LBA- 17: Non-motor symptoms in patients with GTPCH1-deficient dopa-responsive dystonia

Morrison, H., Blackman, J., Gabb, V., Boca, M., Whone, A., Coulthard, E. (Bristol, UK)

Objective: To describe the non-motor features of patients with GTP cyclohydrolase 1-deficient dopa-responsive dystonia (GTPCH1-deficient DRD).

Background: GTPCH1-deficient DRD is a rare disorder (incidence 0.5-1 per million) characterised by young-onset lower limb dystonia with a dramatic and sustained response to low dose oral levodopa. There is limited and contrasting evidence based on small case series describing the frequency and severity of non-motor symptoms.

Method: Patients with confirmed GTPCH1-deficient DRD were prospectively recruited from a tertiary Movement Disorders Clinic or research database at North Bristol NHS Trust. Subjects were evaluated for a range of non-motor symptoms with validated questionnaires and particular focus on mood disturbance, sleep and cognition.

Results: 11 patients (female = 7; male = 4) aged between 26 and 75 years (median = 44 years, IQR 32-62) were recruited from 6 families. Median age at diagnosis was 17 years (IQR 13-43.5). 10/11 (91%) had a dystonic phenotype at presentation and 1/11 adult-onset parkinsonism. 10/11 (91%) of patients were taking levodopa with a mean levodopa equivalent dose of 222mg/day (0-700mg). Motor symptoms were well-controlled in all patients. 6/11 (55%) were taking an antidepressant medication.

Comorbid depression was found in 8/11 (73%) of participants, anxiety in 2/11 (18%), obsessive-compulsive disorder in 2/11 (18%), autism spectrum disorder in 2/11 (18%) and mild learning difficulties in 1/11. 2/11 (18%) had a diagnosis of obstructive sleep apnoea.

Median Generalised Anxiety Scale-7 (GAD-7) score was 7 (IQR 3-10.5) suggestive of mild anxiety and median Patient Health Questionnaire-8 (PHQ-8) score was 12 (4.5-13.5) suggestive of severe depression. Median Global Pittsburgh Sleep Quality Index (PSQI) score was 9/21 (IQR 4.5-10). Mean Montreal Cognitive Assessment (MoCA) score was 25.4/30 (IQR 24-26).

It was observed that depression was more likely to be present in those taking higher doses of levodopa. There was a non-significant trend towards higher PHQ-8 and PSQI scores with increasing dose of levodopa.

Conclusion: There is a high burden of non-motor symptoms in this cohort of GTPCH1-deficient DRD patients, in particular depression and sleep disturbance. Furthermore, there may be unrecognised mild cognitive dysfunction. Deeper phenotyping with neuropsychometric and objective sleep assessment is warranted as these additional symptoms may impact quality of life and be amenable to treatment.

### **LBA-18: Utility of the Virtual Unified Huntington's Disease Rating Scale (vUHDRS®)**

Frank, S. (*Boston, MA, USA*)

Objective: To determine the reliability of administering all sections of the Unified Huntington's Disease Rating Scale (UHDRS®) virtually compared to in-person administration.

Background: The UHDRS®, developed in 1996 by the Huntington Study Group (HSG), is the gold-standard measure to assess Huntington's disease (HD)-related motor, cognitive, behavioral and functional changes. The scale is accepted by regulatory agencies worldwide and is used for clinical and research purposes, but has been only assessed for in-person use. Out of necessity, components of the UHDRS® were used remotely during the Covid-19 pandemic.

Method: Participants with motor manifest HD were recruited if they were at least 18 years old, English speaking, ambulatory and on stable medications. HSG® credentialed sites in the US were utilized to reduce legal, privacy and technology barriers. Selected sites included potential participants from urban, suburban, and rural settings. The complete cognitive, behavioral and functional scales were assessed at an in-person visit, telehealth visit, and second in-person visit, conducted within approximately one month. A complete motor examination was conducted in person twice, but only feasible motor items were assessed virtually. Approximately half of participants were provided a standardized tablet and cellular connection and half used their home-based equipment and internet service. The same personnel performed the assessments in the same order at each visit.

Results: Sixty participants (31 personal equipment, 29 provided equipment) were recruited from 16 sites. One participant did not complete the second in-person visit due to a fall, a serious adverse event unrelated to study activities. The Intraclass Correlation Coefficients (ICC) for the modified motor scores of the telehealth vs. second in person follow-up were 0.93 for personal and 0.95 for provided equipment. For Total Functional Capacity, ICC were 0.94 and 0.93. All measures of cognition, behavior and other functional scales also had ICC consistent with excellent reliability. Examiners reported that eye

movement assessment was the most difficult to perform virtually. As a quality check, the intra-rater reliability of the total motor score between the two in-person visits was high (ICC=0.92;0.93).

Conclusion: Remote administration of all sections of the UHDRS® was safe and feasible, using provided or home-based equipment. The virtual version of this scale can reliably be used for clinical and research assessments.

Acknowledgement or Disclosure: Funded by the HSG. We appreciate the efforts of the patients and study partners in the HD community who participated in this study.

### **LBA-19: Patient-Focused, Clinically Meaningful Endpoints as Evidence of Improved Outcomes and Durability of Effect Following Ulixacaltamide Treatment in Adults with Essential Tremor: Findings from Essential1**

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Objective: A novel, field-first definition of meaningful change in patient-focused Clinical Outcome Assessments (COA) in adults with essential tremor (ET) related to ulixacaltamide (PRAX-944) treatment.

Background: Ulixacaltamide is a selective T-type calcium channel blocker in development for ET. Essential1 (NCT05021991) topline results in adults with ET showed improvement on multiple endpoints including the TETRAS Activities of Daily Living (ADL) and Patient Global Impression of Change (PGI-C) vs placebo at Day 56, and a well-tolerated safety profile. Notably, TETRAS ADL, but not the Performance Subscale, correlated with patient-focused COA. Here we explore ADL as a reliable, patient-centered measure of ulixacaltamide efficacy and durability.

Method: 133 adults with moderate to severe ET were enrolled in Essential1, an 8-week, double-blind, placebo-controlled study with optional Extension. Participants were randomized to ulixacaltamide QAM or placebo followed by blinded lead-in (DBLI; Day 56-99) during which all participants were titrated to ulixacaltamide before transitioning to an open-label period.

Safety and efficacy measures were captured including TETRAS-ADL (and derivate scales including mADL11 – comprising TETRAS-ADL items, excluding social impact, individually scored from 0-3) and PGI-C. Meaningful Score Differences (MSD) capturing clinically meaningful within-patient change in ADL measures were explored using distribution and anchor-based methods with PGI-C as anchor, and corresponding responder analyses conducted.

Results: When examining the magnitude of change in ADL-related scales meaningful to patients, distribution and anchor-based methods yielded similar results, with an MSD consistently defined as  $\geq 2$  points. For mADL11, the MSD was exceeded by 41 (60%) ulixacaltamide vs 14 (40%) placebo-treated participants, with significantly greater proportions of responders observed in treatment arms at higher cutoffs of 3 (55% vs 31%;  $p=0.023$ ) and 4 points (45% vs 23%,  $p=0.028$ ). Sustained improvement and responder rates were observed during the DBLI period for ulixacaltamide-continuing participants and increased for those transitioning from placebo to ulixacaltamide, with no new safety signals.

Conclusion: This is the first time an MSD is defined in ET using a large patient dataset and a focus on measures determined to be most meaningful to patients. We highlight mADL11 as a reliable, patient-focused COA related to ulixacaltamide efficacy and durability, with important decision-making implications for ET therapies.

Acknowledgement or Disclosure: We thank the patients of the Essential1 trial, and our collaborators, including Syneos, the clinical sites and investigators.

### **LBA-20: One-year blinded follow-up of posterior subthalamic stimulation for arm tremor: Secondary endpoints of a randomized controlled crossover trial**

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Objective: To present results from the one-year blinded follow-up of deep brain stimulation (DBS) for arm tremor, which were pre-specified as secondary endpoints of our randomized controlled trial (RCT).

Background: Our published RCT, that compared DBS in the ventral-intermediate thalamic nucleus (VIM-DBS) with the posterior subthalamic area (PSA-DBS) for three months each in a crossover design, was the first to show that PSA-DBS yielded significantly superior suppression of arm tremor(1). Results at one-year follow-up are important to confirm whether the effects from the randomized periods are sustained.

Method: Forty-five patients with isolated or combined arm action tremor received four-level DBS leads (39 bilaterally, 6 unilaterally in dominant hemisphere) covering both VIM (upper two contacts) and PSA (lower two), and were randomized (1:1) to VIM-DBS months 0-3, then PSA-DBS months 4-6, or PSA-DBS first, then VIM-DBS. Primary endpoint: Difference in reduction of Sum dominant arm tremor score (Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS) items 5/6+10-14) of the VIM-DBS versus the PSA-DBS period. The next six months stimulation was optimized at the best contact (location evaluated by imaging). Secondary endpoints (blinded evaluation): Improvement from baseline of sum arm tremor score, face/tongue/voice/head/trunk/lower limb(s) tremor scores, total FTMTRS score, Quality of Life Essential Tremor Questionnaire Summary Index, Visual Analog Scale Global Burden of Disease/Tremor, frequency/severity of adverse events.

Results: The primary endpoint showed significantly greater reduction of Sum dominant arm tremor score in the PSA-DBS period mean paired differences(95% confidence interval) -2.65 (-4.33 to -0.97),  $p=0.002(1.)$  At one-year follow-up, median (25th-75th percentile) Sum dominant arm tremor scores improved from 24(17-27) at baseline to 4(0-9) (p

Conclusion: Blinded follow-up at one year post-surgery confirmed very good and sustained tremor suppression from PSA-DBS for Essential tremor, PD tremor and dystonic tremor, but less so in cerebellar tremor patients.

References.

1. Kvernmo N, Konglund AE, Reich MM, Roothans J, Pripp AH, Dietrichs E, Volkmann J, Skogseid IM. Deep brain stimulation for arm tremor: A randomized trial comparing two targets. *Ann Neurol* 2022; 91:585-601.

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It was investigator-initiated and received no commercial

**Table 1. Secondary endpoints: Paired differences from baseline to the blinded one-year follow-up.**

	Baseline		One year		Paired differences		P
	n	Median(IQR)	n*	Median(IQR)	n	Mean (95% CI)	
FTMTRS dominant arm							
Item 5/6 <sup>a</sup> (0-12)	45	8 (7 - 10)	43	1 (0 - 3)	43	6.6 (5.8 to 7.4)	<.001
Items 10-14 <sup>b</sup> (0-20)	45	13 (10 -18)	43	3 (0 - 7)	43	9.1 (7.6 to 10.7)	<.001
Sum arm (0-32)	45	24 (17 - 27)	43	4 (0 - 9)	43	15.7 (13.8 to 17.7)	<.001
FTMTRS non-dominant arm							
Item 5/6 <sup>a</sup> (0-12)	39	8 (7 - 9)	37	2 (0 - 4)	37	5.5 (4.6 to 6.4)	<.001
Items 11-14 <sup>b</sup> (0-16)	39	10 (8 - 15)	37	4 (1 - 6)	37	6.3 (4.8 to 7.9)	<.001
Sum arm (0-28)	39	18 (14 -24)	37	4 (2 - 9)	37	11.8 (9.8 to 13.8)	<.001
FTMTRS other body regions							
Face/tongue/voice	32	3 (1 - 4)	30	0 (0 - 1)	30	2.4 (1.9 to 2.9)	<.001
Head tremor	26	2 (1 - 3)	24	0 (0 - 1)	24	1.3 (0.9 to 1.8)	<.001
Trunk tremor	11	1 (1 - 2)	9	0 (0 - 0)	9	1.4 (0.7 to 2.2)	.003
Dominant leg	40	2 (2 - 4)	39	0 (0 - 1)	39	1.6 (1.0 to 2.2)	<.001
Non-dominant leg	32	2 (1 - 3)	30	0 (0 - 1)	30	2.0 (1.5 to 2.6)	<.001
FTMTRS Disability arms							
Items 16-21 <sup>c</sup> (0-24)	45	17 (13 - 19)	43	4 (1 - 8)	43	10.5 (8.8 to 12.2)	<.001
FTMTRS total score (0-156)	45	64 (51 -78)	43	12 (5 - 29)	43	43.4 (38.1 to 48.7)	<.001
QUEST SI (0-100)	45	41 (32 - 52)	43	12 (3 - 25)	43	26.7 (22.1 to 31.2)	<.001
VAS GBD Tremor (0-100)	45	82 (74 - 94)	43	20 (9 - 56)	43	49.7 (40.4 to 58.9)	<.001

\* Two complete drop outs during the second randomized phase account for reduced n at the one-year follow-up. (A male patient with advanced multiple sclerosis died from seasonal viral infection, and a woman with dystonic tremor got a stimulator-related infection which necessitated complete device removal).

<sup>a</sup> Items 5/6: sum of arm tremor at rest+postural+kinetic. <sup>b</sup> Item 10: Hand-writing (only scored for dominant arm); item 11-13, Drawing large spiral, small spiral, continuous lines; item 14, Pouring from one plastic cup to the other. <sup>c</sup> Item 16-21: Disability caused by hand tremor (not pre-specified as secondary endpoints, but are shown for complete information.)

Abbreviations: CI – confidence interval; FTMTRS – Fahn-Tolosa-Marin Tremor Rating Scale; IQR – interquartile range; QUEST SI – Quality of Life in Essential Tremor Summary Index; VAS GBD – Visual Analog Scale Global Burden of Disease