Late-Breaking Abstracts

International Congress of
Parkinson's Disease and Movement Disorders®

October 5-9, 2018

HONG KONG

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International Parkinson and
Movement Disorder Society

MDS-0817-4477

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Proof-of-Concept, Double-Blind, Placebo-Controlled Study for CX-8998 a State-Dependent T-Type Calcium (Cav3) Channel Antagonist in Essential Tremor Patients (T-CALM): Efficacy and Safety Results
Spyros Papapetropoulos[1], Margaret S. Lee[1], Stacey Boyer[1], Andrew Krouse[1], Rajesh Pahwa[2], Kelly Lyons[2], William Ondo[3], Hyder A Jinnah[4], Rodger J Elble[5] on Behalf of the T-CALM Investigators (USA)

LBA 01

Nilotinib increases dopamine metabolism and reduces oligomeric: Total alpha-synuclein ratio in Parkinson's disease

F. Pagan, M. Hebron, Y. Torres-Yaghi, A. Lawler, T. Kimbason, N. Starr, B. Wilmarth, M. J. Arrellano, M. Peyton, E. Mundel, N. Yusuf, A. Shekoyan, J. Ahn, C. Moussa (Washington D.C., USA)

Objective: Evaluate the effects of Nilotinib on overall brain dopamine levels and metabolism by measuring CSF for biomarker levels of Homovalinic acid, 3, 4-Dihydroxyphenylacetic acid, oligomeric and total alpha-synuclein levels.

Background: Parkinson's disease (PD) is a neurodegenerative disorder that affects motor and non-motor functions. PD results in loss of dopaminergic neurons as a result of oligomerization and accumulation of alpha-synuclein. Our pre-clinical and open label phase I data indicate that the tyrosine kinase inhibitor (TKI) Nilotinib may improve motor symptoms and cognition, reverse dopamine loss and reduce brain alpha-synuclein. Nilotinib is FDA-approved for the treatment of chronic myeloid leukemia (CML) at 800mg oral dose twice daily.

Method: This is a phase II, open label, random single dose (RSD) study in mid-stage PD patients with mild cognitive impairment (MCI) to evaluate the effects of Nilotinib on disease biomarkers of PD. Cerebrospinal fluid (CSF) from 75 patients was examined to assess changes in the levels of CSF alpha-synuclein and the dopamine metabolite homovanillic acid (HVA) and 3, 4-Dihydroxyphenylacetic acid DOPAC as primary disease biomarkers. A total of 15 patients in each of 5 randomized study groups, including placebo, 150mg, 200mg, 300mg and 400mg Nilotinib had lumbar puncture at 1-4 hours after a single time oral drug administration.

Results: CSF biomarkers analyses showed a statistically significant increase in the level of CSF HVA and DOPAC. No change was detected in total levels of CSF total alpha-synuclien, but lower dose (150mg and 200mg) resulted in a significant decrease of oligomeric; total CSF alpha-synuclein. Further analysis will be performed to compare plasma and CSF levels of these biomarkers between this single time administration and 52-week treatment.

Conclusion: These data suggest that a single time oral administration of Nilotinib may increase brain dopamine levels and metabolism. All patients were receiving a maximum dose of 800mg per day Levodopa therapy and were not receiving any MOA-B inhibitors (selegeline/rasagiline) that may affect HVA levels for at least 6 weeks. These results suggest Nilotinib, in a dose dependent manner, may have a symptomatic effect through modulation of brain dopamine levels. Additionally, the significant reduction of oligomeric alpha-synuclein, which is expected to increase in the CSF of PD patients as the disease progresses, suggests that Nilotinib may reduce misfolded alpha-synuclein accumulation and have a long-term disease modifying effect. Importantly, the dose response of oligomeric alpha-synuclein and HVA changes to nilotinib suggests that the dose administered may depend on the stage of disease to potentially halt PD progression.

LBA 02

Pallidal neural correlates of reward in Parkinson's disease

R. Eisinger, E. Opri, J. Alcantara, M. E. Vazquez, L. Almeida, K. Foote, M. Okun, A. Gunduz (Gainesville, FL, USA)

Objective: Identify neural correlates of reward processing in the pallidum of Parkinson's disease patients.

Background: Reward processing dysfunction in Parkinson's disease (PD) is common and can occur with deep brain stimulation (DBS) of the globus pallidus internus (GPi). Numerous primate studies and a limited number of human studies have identified reward-related single-units in the pallidum, but local field potential studies are lacking.

Method: 10 PD participants undergoing DBS played a modified Go/No-Go reward processing task during surgery after implantation of the macroelectrode into the GPi. In each trial, participants viewed a colored stimulus and either responded (Go) or not (No-Go) based on the prospect for reward (+100 points) or loss avoidance (no-reward: +0 points; loss:-100 points). Participants learned to associate stimuli with

outcomes during preoperative training. During intraoperative game play, monopolar recordings were acquired at each contact of a Medtronic 3387 DBS lead. We searched for neural correlates of reward using spectral decomposition and event related potential (ERPs) techniques. Go and No-Go trials were compared to study neural correlates of movement, and reward and no-reward trials were compared to study neural correlates of reward processing. We examined reward anticipation, action for reward, and reward feedback separately.

Results: We observed prominent decreases in GPi beta band (11-30 Hz) power during movement compared to rest. ERPs were seen in response to stimulus and feedback onset across all trial conditions. There were no differences in ERP or spectral content of signals during stimulus onset between reward and no-reward trials. However, the GPi exhibited significantly higher ERP amplitudes and increased theta (4-8 Hz) power in response to reward feedback. Relative to no-reward trials, we also observed increased beta power in response to reward feedback during No-Go trials.

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LBA 03

Legato-HD Study: A Phase 2 Study Assessing the Efficacy and Safety of Laquinimod as a Treatment for Huntington Disease

R. Reilmann, M. Gordon, K. Anderson, A. Feigin, S. Tabrizi, B. Leavitt, J. Stout, P. Piccini, G. Rynkowski, R. Volkinshtein, J. Savola (Great Valley, PA, USA)

Objective: Evaluate the efficacy and safety of laquinimod in patients with Huntington Disease (HD).

Background: Laquinimod (Teva Pharmaceuticals) is an orally active small molecule that passively enters the blood brain barrier and has been shown to upregulate BDNF secretion and modulate CNS-resident inflammatory pathways involved in pathology of HD. The LEGATO-HD (Laquinimod Efficacy and Safety in a GlobAl Trial Of HD) study originally included three dose arms, 0.5 mg, 1.0 mg and 1.5 mg versus placebo in a 12-month study in patients with HD. Cardiovascular safety concerns were observed in multiple sclerosis studies with laquinimod doses of 1.2 mg and 1.5 mg. Although no similar concern was identified in LEGATO-HD, Teva discontinued the 1.5 mg arm in January 2016 as a precautionary safety measure and continued to evaluate the efficacy and safety of the 0.5 mg and 1.0 mg doses.

Method: LEGATO-HD is a phase 2 multicenter, randomized, double-blind, parallel-group study comparing two doses of laquinimod with placebo. Efficacy assessments include the primary endpoint, change from baseline in Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) at month 12, and the secondary endpoint, the percent change in caudate volume at month 12. Safety measures include adverse event reporting, clinical laboratory tests, vital signs, ECGs, physical examinations, and suicidality (C-SSRS).

Results: LEGATO-HD is fully enrolled with 352 patients randomized and is expected to complete in June 2018. Baseline mean (SD) pooled demographics of enrolled patients include females n=172 (49.1%), males n=178 (50.9%), age 44.4(7.6) years, UHDRS-TMS 24.3(13.1), UHDRS-Total Functional Capacity (TFC) 11.1(1.7), and UHDRS-Functional Assessment (FA) 22.7(2.4). The results of the primary and secondary efficacy endpoints and safety measures will be presented at the conference.

Conclusion: There is a significant unmet medical need to ameliorate the progression of symptoms and the neurodegeneration in HD. LEGATO-HD provides valuable information towards understanding the efficacy and safety of laquinimod as a potential treatment for patients with HD.

LBA 04

Clinical, pathological and genetic determinants of benign PSP

G. Respondek, M. Jecmenica-Lucic, C. Kurz, L. Ferguson, A. Rajput, W. Z. Chiu, J. van Swieten, E. Englund, C. Nilsson, D. Irwin, C. Troakes, S. al Sarraj, E. Gelpi, Y. Compta, J. Schöpe, S. Wagenpfeil, S. Roeber, A. Giese, T. Arzberger (Munich, Germany)

Objective: To identify clinical, pathological, and genetic determinants of survival in PSP. This study involved 186 autopsy-confirmed PSP cases which were recruited from eight brain banks.

Background: Demographic and clinical information was retrospectively reviewed. Symptoms were analysed with respect to their potential association with long (≥ 10 years) and medium or short survival (< 5 years and 5-10 years). Central histopathological analysis and harmonization of staining protocols has been performed. PSP-specific brain lesions were analysed in 36 brain regions and compared between different survival groups. In addition, the survival groups have also been stratified by known SNPs risk allele carrier status.

Method: This study involved 186 autopsy-confirmed PSP cases which were recruited from eight brain banks. Demographic and clinical information was retrospectively reviewed. Symptoms were analysed with respect to their potential association with long (≥ 10 years) and medium or short survival (< 5 years and 5-10 years). Central histopathological analysis and harmonization of staining protocols has been performed. PSP-specific brain lesions were analysed in 36 brain regions and compared between different survival groups. In addition, the survival groups have also been stratified by known SNPs risk allele carrier status.

Results: Of 186 PSP patients with sufficient clinical data, 24 % had a long disease duration of ≥ 10 years (mean: 13.8 [10 – 27] years), while similar percentage of patients (21.5 %) were found to have progressive clinical course of < 5 years (mean: 3.3 [1-4] years). The analysis of timeline and evolution of main clinical milestones revealed different pattern in long duration PSP, compared with both groups of medium and short less survival. The latter groups presented with identical evolution of symptoms. The presence or absence of oculomotor signs in the first 3 years from disease onset was the main predictor of short (< 5 years) or long (≥ 10 years) survival, respectively. Neurodegenerative changes and neuronal tau lesions were most prominent in infratentorial regions, while glial tau lesions showed the opposite pattern with highest density in cortical and subcortical regions. The crucial differences between survival groups were found in the rates of glial tau lesions in cortical, subcortical and infratentorial regions. There was no difference in SNPs risk allele carrier status.

Conclusion: Herein, we described a benign form of PSP with distinctive clinical and pathological patterns. The absence of supranuclear gaze palsy and abnormal saccades in the first 3 years from onset were independent predictors of long duration PSP (≥ 10 years). Our observations suggest that glial pathology plays a crucial role in determining survival in PSP.

LBA 05

Clinical outcomes and STN microelectrode mapping under local and general anaesthesia

S. T. Tsai, T. Y. Chen, S. Y. Chen T. Herrington *(Hualien, Taiwan)*

Objective: The aims of this study were to compare neurophysiological analysis and five-year clinical outcomes of two groups Parkinson's disease (PD) patients after different anaesthetic methods during subthalamic nucleus deep brain stimulator (STN-DBS) implants.

Background: Most STN-DBS for PD are performed under local anaesthesia (LA). STN-DBS under general anaesthesia (GA) is an alternative approach, but optimal methods, impact on clinical outcomes and utility of microelectrode recording (MER) remains uncertain.

Method: 19 consecutive PD patients with similar disability underwent placement of STN-DBS electrodes under either inhalational GA (n = 10) or LA (n = 9). Evaluation included Unified Parkinson's Disease Rating Scales (UPDRS), Mini Mental Status Examination and Beck Depression Inventory. MER were analysed for characteristic gray-white transitions, neuronal spiking and oscillatory dynamics. Clinical follow-up was five years.

Results: Clinical outcomes at five years were similar for both groups. UPDRS part III improved significantly (45.2±17.3% improvement in GA from STN-DBS and 38.1±16.7% in LA) (Table 1). Reduction in dyskinesia and dopamine replacement therapy was similar as well. Cognitive and psychiatric status remained stable and there was no difference in adverse events. Coordinates of active contacts and stimulation parameters were not different between groups. STN firing rates and features were similar between GA and LA. However, distinct dorsolateral beta (13-30 Hz) and ventromedial gamma (30-100 HZ) oscillations were detected in the STN solely for the LA condition. Under general anaesthesia, sub-beta frequency (delta 0.5-4 Hz, theta 4-8 Hz, and alpha 8-12 Hz) oscillations predominated (Figure 1, 2).

Conclusion: Long-term outcomes were equivalent for STN-DBS placed under GA and LA. GA disrupted characteristic beta-frequency spike oscillations, but did not interfere with the detection of dorsal and ventral STN border. Clinically effective, microelectrode-guided STN-DBS under inhaled anaesthesia is a reasonable approach, though larger cohorts are needed to quantitatively assess differences in outcomes.

TABLE 1 (LBA 05)

Table 1 Post-operative DBS effectiveness between GA and LA group

	GA									LA								P-value¶
	Levodopa off DBS off			Levodopa off DBS on			Improvement (%)#			Levodopa off DBS off			Levodopa off DBS on			Improvement (%)#		
	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	
Part I§	5.5	±	2.8	3.3	±	2.3	39.1	±	30.1	4.6	±	1.9	3.2	±	1.4	23.7	±	22.2	0.2282
Part II	29.1	±	8.3	13.7	±	6.3	53.3	±	15.9	20.9	±	8.9	12.6	±	5.7	34.3	±	22.9	0.0512
Part III	56.7	±	12.3	30.7	±	9.6	45.2	±	17.3	43.2	±	13.2	25.4	±	7.0	38.1	±	16.7	0.3764
Brady	21.8	±	4.1	14.6	±	4.4	32.7	±	18.2	18.3	±	4.8	13.4	±	2.9	24.2	±	15.3	0.2933
Tremor	9.8	±	7.8	3.1	±	3.8	57.9	±	35.7	5.8	±	5.5	1.4	±	1.0	51.2	±	40.8	0.7051
Rigidity	11.4	±	3.2	4.9	±	3.2	56.9	±	24.4	8.1	±	3.9	2.8	±	1.9	60.9	±	27.1	0.7386
Posture & Gait	5.0	±	1.1	3.3	±	1.1	33.6	±	21.3	4.3	±	1.2	3.2	±	1.0	21.7	±	23.7	0.2633
Axial	11.6	±	3.7	7.0	±	2.6	37.8	±	22.9	9.2	±	3.2	6.6	±	2.6	25.0	±	22.3	0.2360
Part IV§	5.6	±	2.1	3.6	±	1.6	35.7	±	25.1	5.0	±	1.3	1.7	±	1.2	63.7	±	30.4	0.2522
Total	96.9	±	21.7	51.3	±	14.6	46.3	±	15.0	73.7	±	24.3	42.9	±	13.5	38.4	±	17.8	0.3091
H & Y stage	3.6	±	0.8	2.7	±	0.4	22.6	±	22.8	3.2	±	0.9	2.7	±	0.7	11.9	±	14.9	0.2515
ADL score	44.0	±	22.7	81.0	±	8.8	45.6	±	22.5	65.6	±	19.4	85.6	±	10.1	39.0	±	39.2	0.1258

UPDRS: unified Parkinson's disease rating scale, H&Y: Hoehn and Yahr, ADL: activity of daily living
#Improvement: levodopa off DBS off scores – levodopa off DBS on scores / levodopa off DBS off scores X 100%
§Part I and Part IV scores were compared between pre-operative status with post-operative status at 5 years
¶P-value: t test statistics for improvement (%) between GA and LA groups

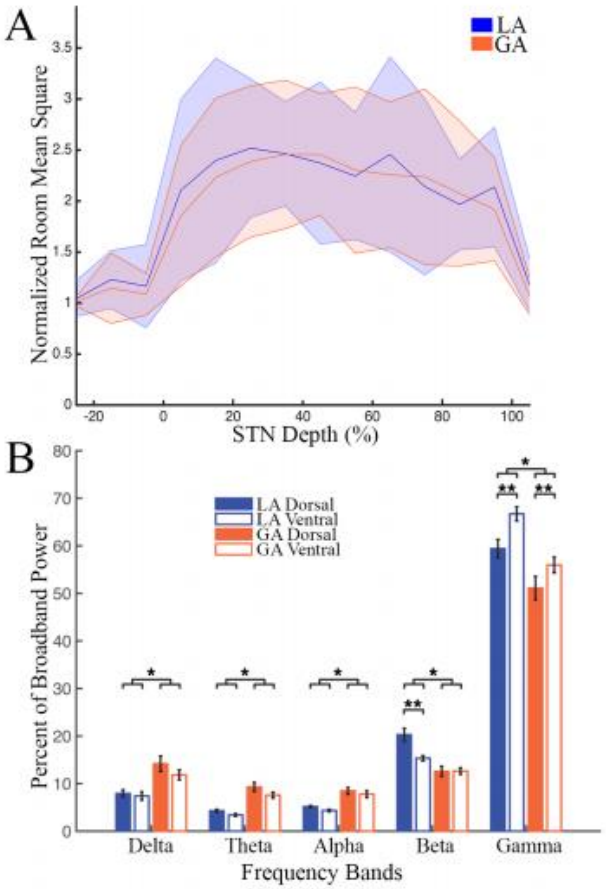

FIG. 1 (LBA 05)

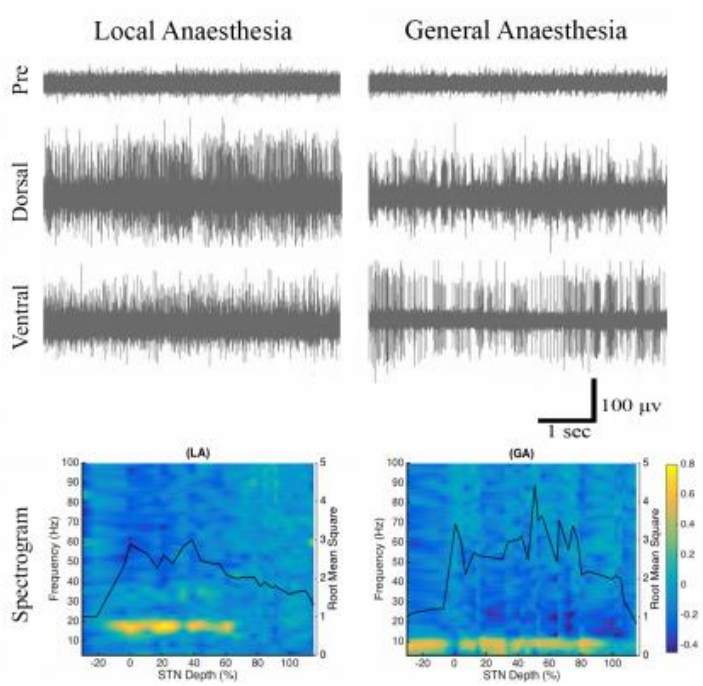

FIG. 2 (LBA 05)

LBA 06

LRP10 genetic variants in familial Parkinson's disease and dementia with Lewy bodies: A genome-wide linkage and sequencing study

W. Mandemakers, M. Quadri, M. Grochowska, H. Geut, E. Fabrizio, G. Breedveld, D. Kuipers, M. Minneboo, L. Vergouw, A. C. Mascaro, E. Yonova-Doing, E. Simons, T. Zhao, A. Di Fonzo, H. C. Chang, P. Parchi, M. Melis, L. C. Guedes, C. Criscuolo, A. Thomas, R. Brouwer, D. Heijsman, A. Ingrassia, G. C. Buonaura, J. Rood, S. Capellari, A. Rozemuller, M. Sarchioto, H. F. Chien, N. Vanacore, S. Olgiati, Y. H. Wu-Chou, T. H. Yeh, A. Boon, S. Hoogers, M. Ghazvini, A. IJpma, W. van Ljcken, M. Onofrj, P. Barone, D. Nicholl, A. Puschmann, M. De Mari, A. Kievit, G. De Michele, D. Majoor-Krakauer, J. van Swieten, F. de Jong, J. Ferreira, G. Cossu, C. S. Lu, G. Meco, P. Cortelli, W. van de Berg, V. Bonifati (Rotterdam, Netherlands)

Objective: The aim of this study was to identify a novel gene implicated in the development of Parkinson's disease (PD), PD-Dementia (PDD), and dementia with Lewy bodies (DLB).

Background: There are clinical, pathological, and molecular overlaps suggesting that PD, PDD and DLB are parts of a continuum of Lewy Body diseases. Yet, in most patients with familial forms of PD, PDD or DLB, variants in the known disease-causing genes (i.e. SNCA, LRRK2) are not found, suggesting that other causative or predisposing genes remain to be identified.

Method: We initially performed genome-wide linkage analysis in an Italian family with dominantly inherited PD (10 affected individuals, average onset age 59·8 years). In the second stage, we sequenced the candidate gene in an international multicenter series of 660 unrelated probands, including 430 clinically diagnosed familial PD (n=420) or PDD (n=10), 62 clinically diagnosed DLB, and 168 pathologically confirmed PD (n=49), PDD (n=74) or DLB (n=45). Sequencing data from 645 individuals with aortic aneurysms (who were not neurologically examined) were used as controls. In the third stage, we screened independent series of clinically diagnosed PD patients and controls with no signs nor family history of PD, PDD and DLB from Sardinia (412 PD, 242 controls), Taiwan (831 PD, 431 controls) and Portugal (223 PD, 138 controls) for specific variants.

Results: We also performed mRNA and brain pathology studies in three patients carrying disease-associated variants. Last, we carried out functional protein studies in in vitro models, including neurons from induced pluripotent stem-like cells. In the initial kindred, we detected significant linkage of PD to chromosome 14, and nominated LRP10 as disease-causing gene. In stage II, among the international series of 660 probands, we identified eight patients (four PD, two PDD, two DLB), who carried different rare, potentially pathogenic LRP10 variants, while only one carrier was found among 645 controls (aortic aneurysms). In stage III, two of the eight variants were detected in three additional PD probands (two from Sardinia and one from Taiwan), but in none of the controls. Out of the total eleven probands with LRP10 variants, ten had a positive family history of disease, and DNA was available from ten affected relatives (in seven of these families). The LRP10 variants were present in nine of these ten relatives, providing independent, albeit limited, evidence of co-segregation with disease. Post-mortem studies in three patients carrying distinct LRP10 variants showed severe Lewy-body pathology. Three of the variants severely affect LRP10 expression and mRNA stability (by cDNA analysis), four other variants affect protein stability (by cycloheximide-chase experiments), and the remaining two variants affect protein localization (by immunocytochemistry), pointing to loss of the LRP10 function as a common pathogenic mechanism.

Conclusion: This work identifies LRP10 pathogenic variants as a novel genetic cause of synucleinopathies. Elucidating the function of the LRP10 protein can offer novel insights into mechanisms, biomarkers and therapeutic targets.

LBA 07

A double-blind, delayed start trial of levodopa in Parkinson's disease

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Objective: The aim of this study was to investigate if levodopa has a disease modifying effect on Parkinson's disease symptoms and functional health.

Background: Levodopa is the mainstay for the treatment of Parkinson's disease. It is not known whether levodopa has a disease-modifying effect. Resolving this burning clinical question will provide guidance when to start with levodopa.

Method: In a randomized, delayed-start, double-blind, placebo-controlled, multi-center trial, patients with Parkinson's disease without limitations in functional health were assigned to 80 weeks of treatment with levodopa/carbidopa 100/25 mg TID or to 40 weeks placebo TID followed by 40 weeks levodopa/carbidopa TID. There were 8 assessments: at baseline and at four, 22, 40, 44, 56, 68, and 80 weeks. The primary outcome measure was the difference in the mean total Unified Parkinson's Disease Rating Scale (UPDRS) scores between the early- and delayed-start groups at 80 weeks. Secondary outcome measures were rate of change in UPDRS scores, functioning in daily life measured with the AMC Linear Disability Score, disease related quality of life measured with the Parkinson's Disease Questionnaire-39, and complications of treatment. In order to be able to detect a minimal clinical relevant difference of 4 points on the total UPDRS at 80 weeks 446 newly diagnosed patients were included.

Results: From 17 August 2011 to 17 May 2016, a total of 446 patients were enrolled. 222 patients were assigned to the early-start group, and 223 patients were assigned to the delayed-start group. The last assessment was done in November 2017. Data is still being analyzed. Final results will be presented at the congress.

Conclusion: The LEAP-study will provide insights into the possible disease modifying effects of early levodopa.

LBA 08

Proprioceptive Focal Stimulation (Equistasi®) may improve quality of gait in middle-advanced Parkinson's disease patients. Double-blind, double-dummy, randomized, crossover, Italian Multicentric study

A. Peppe, P. Paone, S. Paravati, M. G. Baldassarre, L. Bakdounes, F. Spolaor, A. Guiotto, D. Pavan, Z. Sawacha, D. Clerici, N. Cau, A. Mauro, G. Albani, M. Avenali, G. Sandrini, C. Tassorelli, D. Volpe (Roma, Italy)

Objective: Object of the study was to evaluate the efficacy of propriocettive Focal Stimulation on Gait in middle – advanced Parkinson (PD) patients by a crossover, randomized, double Blind double dummy study using Equistasi®, nanotechnological device of the dimension of a plaster which generates High Frequency segmental vibration.

Background: The efficacy of Gait Analysis (GA) on evaluating gait modification on Parkinson's Disease (PD) Patients (1) is already well known. On the other hand, several studies have shown that Proprioceptive Focal Stimulation seems to be useful in symptoms amelioration in several neurological disease. Therefore, GA was recorded in a group of PD patients in randomized blind double dummy study using Equistasi ® device and its placebo (inactive plaque).

Method: Forty PD patients (age 68, 7 years, Duration disease 8.34 years, Duration Therapy 7,3 years; H&Y 2.52) at their best on therapy, were enrolled in the study. They were randomized. Four GA (before and after either active and placebo device) were performed always at the morning. Three plaques devices were put on the skin for 12 weeks: one at C7, one at the right and the left leg, on soleus muscle (2) Equistasi® is a nanotechnological device of the dimension of a plaster which generates High Frequency segmental vibration. Clinical state was monitored by MDUPDRS part III. Parametric (One-way ANOVA and paired t-Student) and not – parametric statistic (Freidman ANOVA and Wilcoxon test) were used.

Results: The analysis of the Spatial –Temporal variables showed a significant improvement of Mean Velocity (MV) p=.006, Stride Lenght (SL) in right and left respectively p=.003 and p=.005, Stance (STA) in right and left respectively p=.026 and p=.040 and Double Support Stance (DSS) in left and right stride respectively p=.036 and p=.007, in Active evaluation. Moreover, these parameters were more significant in the most compromised patients (H&Y=3). MDUPDRS Part III was statistically reduced both in Active and Inactive device evaluation (Active: p=0.000; Inactive: p=0.003), but items 3.10, 3.12 and 3.13 were statistically reduced only in the Active treatment.

Conclusion: The results, in this group of patients, encourage to investigate the mechanical focal vibration as stimulation of proprioceptive system in PD. The effect of the device on more severe patients may open a new possibility to the management of this stage of PD. Over the influence on postural stability previous reported, the present study indicates as the device ameliorates also gait performance, and confirms the support that GA gives to underlight the modifications of gait in PD patients.

References: 1) Does gait analysis quantify motor rehabilitation efficacy in Parkinson's disease patients?Peppe A, Chiavalon C, Pasqualetti P, Crovato D, Caltagirone C. Gait Posture. 2007 Sep; 26 (3):452-62. Epub 2007 Jan 19. 2) A wearable proprioceptive stabilizer (Equistasi®) for rehabilitation of postural instability in Parkinson's disease: a phase II randomized double-blind, double-dummy, controlled study. Volpe D, Giantin MG, Fasano A.PLoS One. 2014 Nov 17; 9 (11).

LBA 09

Synaptic pathology of cerebellar climbing fibers regulates cerebellar oscillations and motor rhythms in essential tremor

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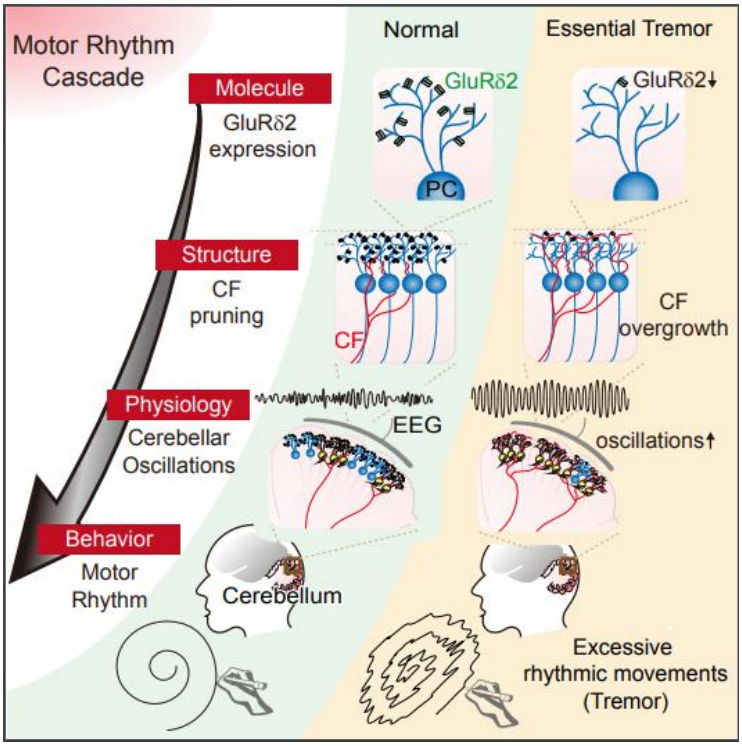
Objective: To identify a pathophysiology of essential tremor.

Background: Essential tremor (ET) is one of the most common movement disorders, affecting 4% of individuals aged 40 years or older, yet the pathophysiology of ET remains unknown.

Method: We examined postmortem cerebellum in ET patients and age-matched controls to identify ET-linked pathological changes. We used pathology-driven mouse model to prove the causal relationship between pathology and ET-like tremor. We used the tremor mouse model to identify the real-time mechanism of tremor generation in cerebellum via in-vivo electrophysiology, optogenetic and pharmacological methods. Finally, we developed a new methodology named cerebellar electroencephalography (cEEG) to validate the mouse discovery back to ET patients.

Results: We observed climbing fiber (CF) synaptic pruning deficits in postmortem cerebellum in ET patients, and the synaptic deficits are correlated with GluRδ2 deficiency in the cerebellum. Mice with cerebellar GluRδ2 deficiency (ΔGluRδ2) recapitulate similar CF pathology and develop adult-onset, chronic and kinetic-only tremor mimicking ET. Interrogations in the mouse model identified that CF synaptic pathology leads tremor via abnormal cerebellar oscillations. Using cEEG technology, we confirmed that abnormal cerebellar oscillations also exist in ET patients and could be a physiological signature with immediate clinical application.

Conclusion: We identify a pathophysiology of ET, with matched mouse and human evidence spanning molecular (GluRδ2), structural (CF synaptic pathology), physiological (abnormal cerebellar oscillations) and behavioral (tremor) levels.



GRAPH 1 (LBA 09)

Figure 1

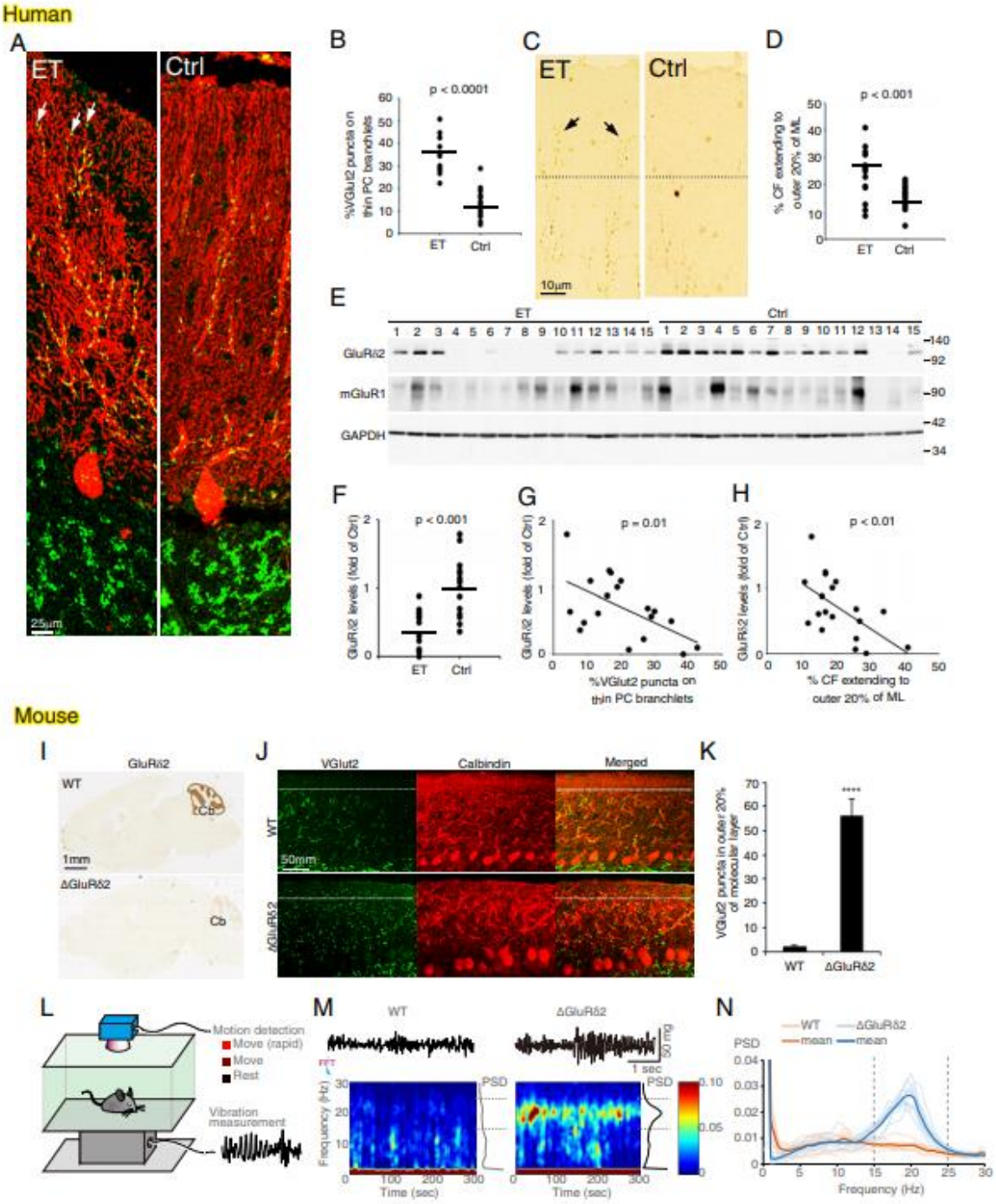


Figure 1. CF synaptic pathology and corresponding GluRδ2 reduction in the postmortem cerebellum of ET patients leads to the development of ΔGluRδ2 tremor mouse model.

FIG. 1 (LBA 09)

Figure 2

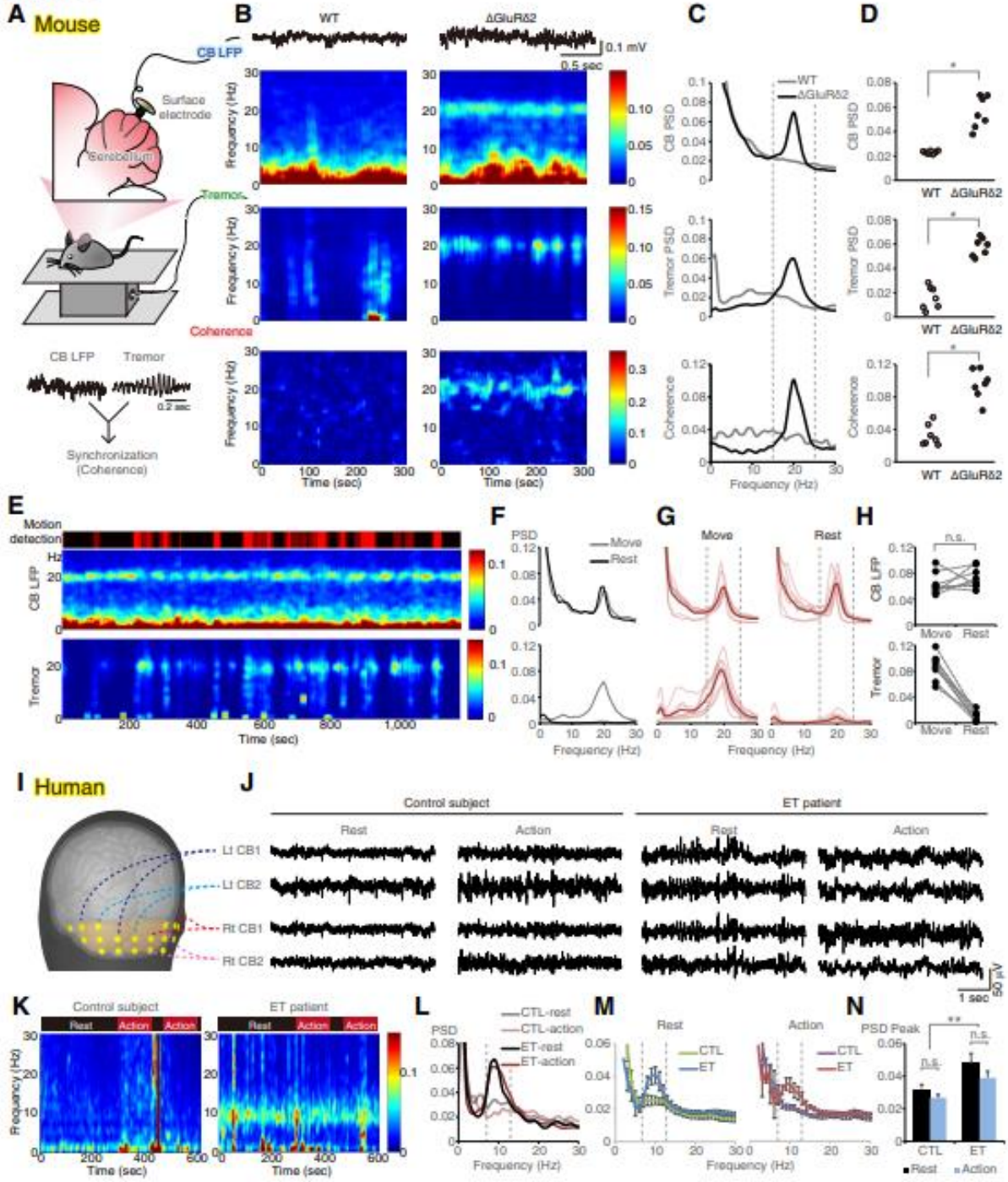


Figure 2. In-vivo electrophysiology in ΔGluRδ2 mice leads to the discovery of excessive cerebellar oscillations in ET patients.

FIG. 2 (LBA 09)

LBA 10

Nonmotor Symptoms, Quality of Life, and Tolerability/Safety With Long-term Levodopa-Carbidopa Intestinal Gel Treatment in Advanced Parkinson's Disease Patients – Interim Data from the Multinational Observational Long-Term Study DUOGLOBE

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Objective: Evaluate long-term safety and effectiveness of levodopa-carbidopa intestinal gel (LCIG) treatment on nonmotor symptoms (NMS) and quality of life (QoL) in advanced Parkinson's disease (PD) patients.

Background: LCIG has been shown to improve QoL and NMS in advanced PD patients. However, prospective, long-term data from multinational studies of LCIG's effect on NMS, QoL, and the safety profile in routine clinical practice are limited.

Method: DUOGLOBE is the first multi-country (including US) observational routine care study of LCIG with a 3-year follow-up. NMS were assessed using NMS Scale (NMSS), Epworth Sleepiness Scale (ESS), and PD Sleep Scale-2 (PDSS-2); QoL was assessed using 8-item PD Questionnaire. Serious adverse events (SAEs) were assessed. Outcomes were collected at baseline, day 1 of LCIG, and months (M) 3, 6, and 12 for this interim analysis.

Results: The safety dataset included 139 patients from 10 countries. At M12, 35% were on LCIG monotherapy. LCIG treatment led to improvements in NMS, daytime sleepiness, and sleep quality (lower NMSS, ESS and PDSS-2 scores at M12). [Figure1] NMSS subdomains sleep/fatigue, mood/cognition improved the most, and significantly through M12. QoL significantly improved through M12; not dependent on gender, age, or disease duration.[Figure2] Modified Caregiver Strain Index Score significantly improved until M6.[Figure3] When comparing patients who completed 6M of treatment with those who did not, baseline demographics were similar with slightly higher mean age, Hoehn & Yahr stage, and lower mean weight in the non-completer group.[Table1] Overall, 28% experienced SAEs, 11% AEs that led to discontinuation.[Tables2 – 4] Higher age, but not gender and disease duration, led to more SAEs (31% vs. 17%).

Conclusion: In this interim analysis of the first multinational observational study with LCIG over 3 years, LCIG demonstrated improved QoL and NMS burden including mood and sleep. The safety and tolerability in routine clinical practice was consistent with the phase 3 study program, with low discontinuation rates, and no predictors for SAEs except advanced age. These findings demonstrate a positive long-term benefit-risk profile for LCIG treatment of NMS in advanced PD patients.

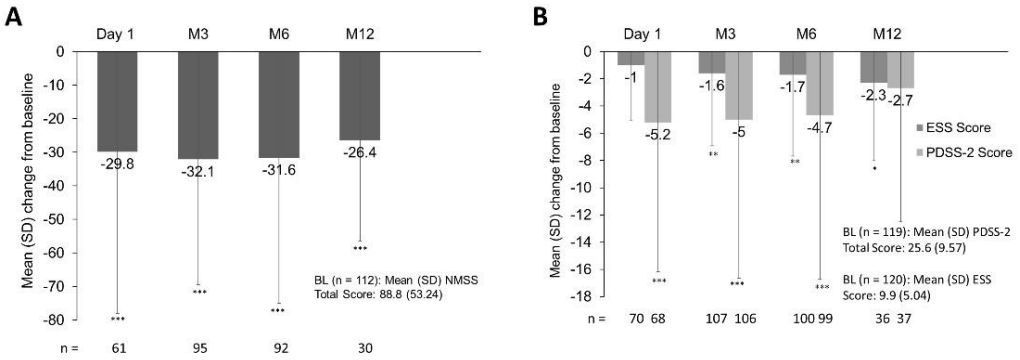

Figure 1. Mean (SD) change from baseline at regularly scheduled visits in NMSS symptoms as assessed by (A) NMSS; (B) PDSS-2 and ESS scores. Effectiveness assessments were only collected at day 1 for patients with prior treatment during the temporary use of a nasojejunal tube. BL = baseline; ESS = Epworth Sleepiness Scale; M = month; NMSS = Non-motor Symptom Scale; PDSS-2 = Parkinson's Disease Scale; SD = standard deviation. ***, **, * statistically significant at $P < .001$, $P < .01$ and $P < .05$ respectively.

FIG. 1 (LBA 10)

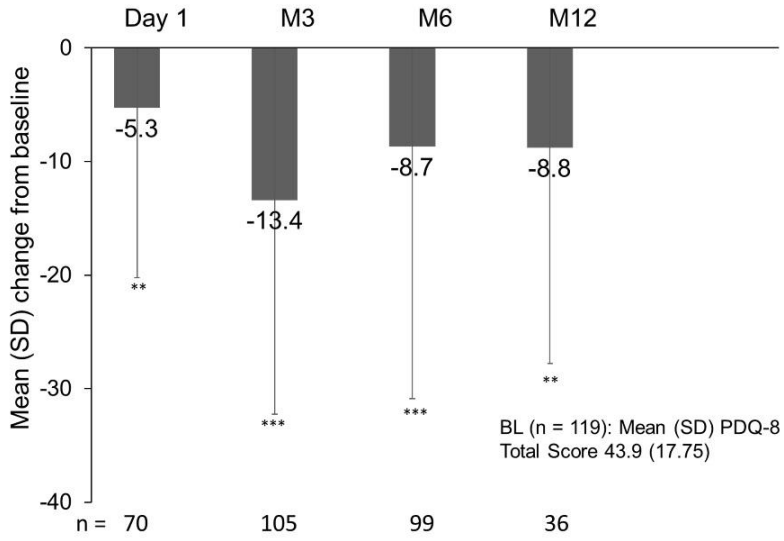

Figure 2. Mean (SD) change from baseline at regularly scheduled visits in QoL symptoms as assessed by PDQ-8 total scores. Effectiveness assessments were only collected at day 1 for patients with prior treatment during the temporary use of a nasojejunal tube. BL = baseline; M = month; PDQ-8 = Parkinson's Disease Questionnaire-8; SD = standard deviation. ***, ** statistically significant at $P < .001$ and $P < .01$ respectively.

FIG. 2 (LBA 10)

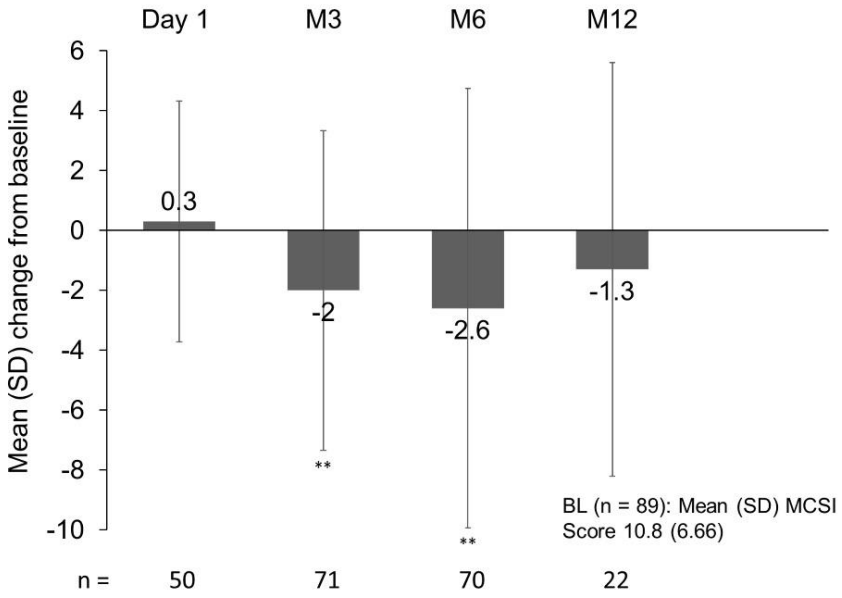

Figure 3. Mean (SD) change from baseline at regularly scheduled visits in caregiver burden as assessed by MCSI scores. Effectiveness assessments were only collected at day 1 for patients with prior treatment during the temporary use of a nasojejunal tube. BL = baseline; M = month; MCSI = Modified Caregiver Strain Index; SD = standard deviation. ** statistically significant at $P < .01$.

FIG. 3 (LBA 10)

TABLE 1 (LBA 10)

Table 1. Baseline demographics

	Mean (SD)	
Parameter	**6-month completers**	**Non-completers**
Age (years)	70.1 (8.06)	73.1 (8.34)
Weight (kg)	72.9 (12.94)	66.6 (14.75)
Hoehn & Yahr	2.9 (0.79)	3.6 (0.79)

SD = standard deviation

TABLE 2 (LBA 10)

Table 2. Study Discontinuations

	Patients, n (%) N = 139
Discontinuations due to primary reasons	**29 (20.9)**
Adverse events	14 (10.1)
Withdrew consent	3 (2.2)
Lost to follow up	2 (1.4)
Other*	10 (7.2)

* Other reasons for discontinuation in 2 or more patients include: lack of efficacy, inconvenience of the system, and violation of exclusion criteria.

TABLE 3 (LBA 10)

Table 3. Adverse Events

	Patients, n (%) N = 139
Subjects with:	
Any serious AE	39 (28.1)
Any severe AE	30 (21.6)
Any SAE with reasonable possibility of causal relationship to LCIG	13 (9.4)
Any AE leading to drug being withdrawn	15 (10.8)
Deaths	6 (4.3)
Deaths considered to be related to the treatment by the study investigator	1 (0.7)

AE = adverse event; LCIG = levodopa-carbidopa intestinal gel; SAE = serious adverse event.

TABLE 4 (LBA 10)

Table 4. Treatment-Emergent Serious Adverse Events*

	Patents, n (%) n = 139	
	SAEs	Treatment-related SAEs (Reasonable Possibility)
Patients with any SAE	39 (28.1)	9 (6.5)
SAEs occurring in >1% of patients		
Fall	3 (2.2)	1 (0.7)
Pneumoperitoneum	3 (2.2)	2 (1.4)
Abdominal pain	2 (1.4)	1 (0.7)
Anemia	2 (1.4)	0
Decubitus ulcer	2 (1.4)	0
Device occlusion	2 (1.4)	2 (1.4)
Femoral neck fracture	2 (1.4)	0
General physical health deterioration	2 (1.4)	1 (0.7)
Peritonitis	2 (1.4)	1 (0.7)
Pneumonia	2 (1.4)	0
Procedural pain	2 (1.4)	1 (0.7)
Urinary tract infection	2 (1.4)	0

LBA 11

Predictive Validity of Level I PD-MCI Criteria, using Global Cognitive Screeners, for PDD

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Objective: PD-MCI can be used as a descriptive entity for clinical and research purposes and the PD-MCI criteria1 need to be validated. The objective is to assess the predictive validity of Level I MDS PD-MCI criteria, using global cognitive screeners, for PDD.

Background: Our analyses regarding Level II2 and Level I3 showed a contribution of PD-MCI to the hazard of PDD amongst other clinical variables. The predictive value of global cognitive screeners still needs to be evaluated and compared to Level I and II.

Method: This retrospective study combined 4 large datasets. Conversion to PDD was the primary outcome. A Cox model was used to evaluate whether Level I PD-MCI based on a global cognitive screener at baseline adds to the risk of PDD as estimated by age, gender, level of education, disease duration, UPDRS-III, and depression. Either the MMSE (cut-off of

Results: Follow-up data on 467 PD patients were available. The mean age was 68.7 years (SD 8.8), median duration since PD symptom onset was 4.0 years (IQR 2.0-8.0), and median UPDRS-III total score was 20 (IQR 13-28). A total of 69 patients developed PDD during follow-up (14.3%). Preliminary analyses indicate a clear contribution of MMSE and MoCA scores to the hazard of PDD, i.e. MMSE/MoCA scores below the cut-off resulted in significantly higher hazard ratios. Additional analyses, the comparison of the current analyses to Level I and II, will still be performed and will be presented at the congress.

Conclusion: N/A

LBA 12

Preliminary Report on the Safety and Tolerability of Bone marrow-derived Allogeneic Mesenchymal Stem Cells infused intravenously in Parkinson's disease Patients

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Objective: The primary objective of this study is to prove safety and feasibility in the use of allogeneic mesenchymal stem cells (MSC) purified from bone marrow derived from a healthy adult and delivered intravenously in escalating doses to patients with idiopathic Parkinson's disease (PD).

Background: Considerable evidence supports a critical role of chronic neuroinflammation in the degenerative process of PD. Through paracrine and exosome actions MSC possess regenerative and immunomodulatory properties that can restore immune system homeostasis.

Method: We recruited 20 subjects between 45 and 75 years of age who meet the UK Brain Bank criteria for idiopathic PD and who have a Hoehn and Yahr of.

Results: To date, a total of 10 patients (5 PD patients in the 1 and 3 x 10 6 dose cohorts) have received a single IV infusion without any adverse reactions in the first 24 hours. In subsequent follow up the most common side effect was hypertension (30%), which was mild and transient in all cases, not requiring treatment. All five patients in the first dose cohort sustained a reduction in UPDRS-III motor score (OFF state) at 3 and 12 weeks follow up. There was no difference in MSC tolerability between subjects with and without dopaminergic treatment.

Conclusion: Preliminary findings from this ongoing small proof-of-concept study demonstrates that MSC infusion at dosages 1 X 106 MCS/kg and 3 X 106 MCS/kg appear to be safe and well tolerated in subjects with mild to moderate Parkinson's disease. Clinically, there is a trend toward improvement in the OFF state motor scores, but this should be interpreted with caution based on both the limited data and the purpose of the study. Our preliminary results warrant the completion of the study with the goal of identifying an ideal, well-tolerated dose that is associated with improvement in cognition, motor function, disability, and ADL.

TABLE 1 (LBA 12)

Table 1. Patient's Demographics		
Group	**A**	**B**
Dose of MSC/kg	1×10^6	3×10^6
Number of subjects	5	5
Gender, Female to Male ratio	3:2	2:3
Age (yr), mean (SD)	64.4 (8.5)	67.4 (5.9)
DOD (yr), mean	5.9 (1.4)	5.8 (1.6)
Race (n), % (Caucasian, Hispanic, Asian, African-American and Native American)	Caucasian: 4 (80%) Asian: 1 (20%)	Caucasian: 4 (80%) African-American: 1 (20%)
MOCA, mean (SD)	27 (1.8)	28 (1.7)
UPSIT, mean (SD)	25.8 (6.3)	15.4 (6.6)
UPDRS-T, mean (SD)	52.4 (15.8)	48.6 (23.4)
UPDRS-M, mean (SD)	32 (7.0)	36.2 (18.1)
H&Y, mean (SD)	1.7 (0.6)	2 (0.7)

Abbreviations: MSC, mesenchymal stem cells; DOD, disease duration; MOCA, Montreal Cognitive Assessment; UPSIT, University of Pennsylvania Smell Identification Test; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr Staging

TABLE 2 (LBA 12)

Table 2. Adverse Events after Infusion visit

Adverse Reaction		N=10	Details	AE Relationship
Constitutional	Fall	20%	Mild	Unrelated
Infections	URI	20%	Mild and transient	Unrelated
	Bronchitis	10%	Required antibiotic treatment	Unrelated
	Sinusitis	10%	Required antibiotic treatment	Unrelated
	HIV	10%	Required antiviral treatment	Unrelated
Cardiovascular	Hypertension	30%	Mild and transient	Probably related
	Chest pain	10%	Mild and transient	Unlikely related
Gastrointestinal	Nausea	20%	Baseline symptoms, Mild and transient	Unrelated
	ABD Bloating	10%	Baseline symptoms, Mild and transient	Unrelated
	Constipation	10%	Mild and transient	Unrelated
	GERD	10%	Mild and transient	Unrelated
Musculoskeletal	Arthralgia	20%	Baseline dx of Arthritis	Unrelated
Integumentary	Rash	10%	Baseline dx of Dermatitis	Unrelated
	Dry skin	20%	Baseline dx of Dermatitis	Unrelated
	Bruising	10%	After Falling	Unrelated
	Face flushing	10%	Mild and transient	Possibly related
Neurologic	Headache	10%	Mild and transient	Unrelated
	Dyskenesia	10%	Increase	Possibly related
	Tremor Increase	20%	Subjective	Possibly related
Psychiatric	Panic attack	10%	Baseline dx of Anxiety	Unlikely related
	Sadness	10%	Mild and transient	Unrelated
	Anxiety	20%	Required treatment	Unrelated
Laboratory	WBC	10%	Transient increased	Unrelated
	Total Lymphocyte Count	20%	Transient decreased	Possibly related
Infusion: one patient reported Neck pain and another patient reported Headache, both symptoms were mild, transient and did not require any treatment				

Abbreviations: URI, upper respiratory infection; HIV, human immunodeficiency virus; GERD, Gastroesophageal reflux disease; WBC, white blood cells.

TABLE 3 (LBA 12)

Table 3. Secondary Outcomes

			Rating Scales (OFF state)						Self-assessment	
Patient	Levodopa response	Visit	UPDRS -I	UPDRS -II	UPDRS -III	UPDRS -IV	UPDRS Total	TUG	ADL	PDQ-39
A01	74%	*Screening*	5	10	31	2	48	18.1	70%	45
		Week 3	3	6	9	2	20	17.56	80%	45
		Week 12	4	6	14	1	25	14.82	80%	71
A02	63%	*Screening*	3	23	41	11	78	13.08	90%	42
		Week 3	0	4	14	7	25	13.06	90%	33
		Week 12	3	7	26	3	39	12.53	80%	30
A03	44%	*Screening*	0	13	34	0	47	15.78	100%	18
		Week 3	1	5	25	0	31	14.25	100%	20
		Week 12	0	7	32	0	39	15.06	100%	23
A04	80%	*Screening*	2	13	36	8	59	29.98	80%	61
		Week 3	2	7	27	1	37	15.26	80%	36
		Week 12	3	5	13	8	29	19.66	90%	10
A05	70%	*Screening*	1	7	20	2	30	11.88	100%	11
		Week 3	2	3	16	2	23	12.15	100%	24
		week 12	2	8	17	0	27	11.9	80%	32
B06	80%	*Screening*	2	7	36	3	48	17.75	80%	33
		Week 3	2	4	10	2	18	15.09	100%	12
B07	73%	*Screening*	2	7	38	1	48	22.43	90%	10
		Week 3	2	4	16	0	22	21.09	100%	8
B08	52%	*Screening*	3	16	65	2	86	28.23	70%	83
		Week 3	1	5	43	1	50	18.98	80%	66
B09	83%	*Screening*	2	11	24	2	39	14.4	90%	23
		Week 3								
B10	61%	*Screening*	0	4	18	0	22	15.86	100%	4
		Week 3								

Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; TUG, Timed Up and Go; ADL, Activities of daily living ; PDQ-39, Parkinson's Disease Questionnaire – 39.

LBA 13

EPG5-associated Vici syndrome as a potential candidate gene for recessive early-onset parkinsonism

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Objective: The aim of the study is to identify new genes involved in autosomal recessive early-onset parkinsonism, using consanguineous families and applying whole genome genotyping and Next Generation Sequencing (NGS) technologies.

Background: Parkinson disease (PD) affects 1-2% of the population over the age of 65. It is characterized by impaired balance, bradykinesia, rigidity and resting tremors. To date, more than 10 validated genes have been identified, associated with either autosomal dominant (AD) or recessive (AR) forms of PD. However, the identified genes associated with early-onset (EO, ≤40 years) AR PD only explain 25% of PD cases, thus, a significant proportion of PD cases remain genetically unexplained.

Method: From a series of 160 consanguineous families of multi-ethnic origins, we identified a family with 2 unaffected first-cousins parents and 3 affected offspring in which both linkage analysis using whole-genome genotyping on DNA microarrays (Illumina Infinium OmniExpress) and exome sequencing (Roche KAPA V3.0 and Illumina NextSeq 500 sequencer) were performed.

Results: Linkage analysis identified a single region of linkage (LOD-score=2.4) on the chromosome 18q12.3-18q21.1. After variant filtering steps of exome sequencing, keeping only those heterozygous in both unaffected parents and homozygous in the 3 affected children, it remained only one rare variant in EPG5, located in the linkage region. This missense mutation in EPG5 (c.5307C>A; p.Phe1769Leu), absent from GnomAD public database, highly conserved through species, was predicted to affect the mRNA splicing that was further validated using patient fibroblast. RT-PCR and western blot showed a deletion of 55 nucleotides leading to a premature frameshift and a strong decrease of EPG5 expression in the patient fibroblast. Recessive mutations in EPG5 encoding ectopic P-granules autophagy protein 5 are already known to cause Vici syndrome, a severe, EO neurodevelopmental disorder. All the 3 EPG5 patient carriers showed no Vici syndrome signs, but EO parkinsonism (31-37 years), rapid and severe disease progression, pyramidal signs, dementias and severe psychosis after 4 years of duration, dystonia and cerebellar ataxias.

Conclusion: We identified a strong candidate gene for AR PD, EPG5 that has a key role in autophagy in multicellular organisms, one of the functions already known to be implicated in PD. Further functional and modelling data are needed to strengthen the role of this gene in PD.

LBA 14

Functional near infra-red spectroscopy neuroimaging of prefrontal cortex in Parkinson's disease during cognitive tasks under different postures

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Objective: To determine how prefrontal cortex activation is affected during concurrent cognitive and balance tasks.

Background: In Parkinson's disease (PD) reduced executive function is associated with poorer quality of life, decreased activities of daily living and increased balance and gait disturbance. Neural circuits involving prefrontal cortex and involved in executive function are critical for control of balance and gait.

Method: Pre-frontal cortex alterations in concentration of oxy- (O2Hb) and deoxy-haemoglobin (HHb) in cerebral microcirculation blood vessels were recorded using fNIRS during performance of a cognitive task (verbal fluency) involving executive function. During this task, participants were either seated or standing quietly on a force plate. Early stage PD (N=14; 64 yrs), healthy age matched controls (N=17; 64.8 yrs), and young participants (N=12; 25 yrs) were assessed according to the following protocol repeated 5 times during sitting and standing: Baseline - no activity (30s), Verbal Fluency (30s), Recital of days of the week (30s).

Results: All groups had similar performance in the verbal fluency and the week day recital tasks. In the young group, neuronal activation during the verbal fluency task (relative to baseline) was characterised by an increase in O2Hb and a decrease in HHb in the right dorsolateral prefrontal cortex (DLPFC) while seated and in the DLPFC bilaterally during standing. Similar, but reduced changes were observed for the age-matched control group. For the PD group there was a bilateral increase in DLPFC O2Hb during the seated condition but this was greatly reduced in amplitude. During standing there was negligible change in DLPFC O2Hb in both hemispheres for PD participants. There was negligible change in O2Hb during the week day recital task for all groups.

Conclusion: These changes in O2Hb indicate that PD participants have reduced activation of the DLPFC during the performance of cognitive tasks involving executive function. During standing activation of the DLPFC is further reduced, in contrast to young and control participants who have increased bilateral activation. This indicates that people with PD have either reduced activation of the same neural circuits or utilize different neural circuits to complete these tasks.

LBA 15

Subthalamic Nucleus Activity Encodes Aspects of Speech Production in Subjects with Parkinson's Disease

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Objective: Our overall goals are to determine how speech information is encoded at multiple levels within the basal ganglia-cortical network, and to determine the relationship between this neural activity and vocal output in movement disorders patients.

Background: Speech production is disrupted in Parkinson's disease (PD), yet roles of the basal ganglia in speech are poorly understood. Deep brain stimulation (DBS) is the only setting in which basal ganglia recordings can be obtained while a person speaks.

Method: To explore how speech features are encoded in the corticosubthalamic circuit, simultaneous recordings of subthalamic nucleus (STN) units, STN local field potentials (LFPs), electrocorticography (ECoG), and spoken utterances were obtained in 14 subjects with PD, during DBS lead implantation. At different recording depths in the STN, subjects read aloud 3-phoneme words and pseudowords presented on a computer screen, with the initial consonant of the stimuli involving articulation primarily with the tongue or the lips. We examined the relationship of 1) STN unit firing to speech cue and onset, 2) STN LFPs to articulation with lips vs. tongue, and 3) STN LFPs to the formant ratio, an indirect acoustic measure of gain in speech articulation.

Results: Half of 79 STN unit recordings exhibited firing rate modulation. Trial-to-trial timing of changes revealed that locking to cue presentation was associated with decreases in firing rate, while locking to speech onset was associated with increases in firing rate. Speech-related increases in high gamma activity were found in most of the 88 STN LFP-recording locations, ~1/3 of which exhibited a significant effect of articulator type (tongue or lips). The greatest changes in gamma power occurred more dorsally, but without evidence for the articulator type topography observed in simultaneous ECoG. In addition, STN theta power positively predicted the magnitude of the formant ratio during speech, while STN beta power was a negative predictor.

Conclusion: These unique data indicate that STN neuron activity is dynamic during the production of speech, reflecting temporally-dependent inhibition and excitation of separate populations of neurons. The results also provide evidence for involvement of the STN in speech production at the level of articulatory features, including contributions to gain adjustment of articulatory movements. Overall, these studies are the first to establish a role for STN activity in encoding aspects of speech production. This foundation will enable extended exploration of basal ganglia function in speech, aimed at informing future DBS strategies targeted to dysfunctional speech production in movement disorders.

LBA 16

Long-term intake of Mucuna pruriens in drug-naïve Parkinson's disease in sub-Saharan Africa: A multicentre, non-inferiority, randomised, controlled clinical trial

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Objective: (1) To describe a 52-week multicenter trial (still ongoing) comparing the long-term efficacy and tolerability of Mucuna pruriens (MP) powder vs. Levodopa/Benserazide 200+50mg (LD+BZ) in patients with Parkinson's disease (PD) never treated with Levodopa. (2) To describe MP-induced improvement of symptoms usually considered non-levodopa-responsive (postural instability, dysphagia) in a few cases with longstanding disease. (3) To provide insights on the feasibility of cultivating MP plants in patients' own garden and in hospital backyards.

Background: In low-income countries, the access to levodopa is limited and patients with PD are often undertreated/untreated with great limitations in their quality of life and survival.

Method: In this phase-2 prospective study (started in February 2018) involving 3 Ghanaian hospitals, we aim to recruit 90 patients diagnosed with idiopathic PD to be randomized to receive either MP powder or LD+BZ in a parallel-group, non-inferiority study design. Individual daily dose was calculated considering that (i) the Levodopa content in Ghanaian MP powder was 6.3% (calculated a priori in Milan), (ii) a 5-fold conversion factor is needed due to the lack of a DDCI in MP, and (iii) body weight. Hence, 100mg of LD+BZ corresponds to 8 g of MP powder. The primary endpoint is the non-inferior change in quality of life (measured by the PDQ-39) induced by MP as compared to LD+BZ. In addition, patients are assessed using the UPDRS parts I-to-IV, the Hoehn & Yahr stage, adverse events forms. Informed consent and Ethical Committee approvals have been obtained. This trial is registered at the Pan African Clinical Trial Registry, ID: PACTR201611001882367.

Results: After the first 3 months, 26 patients have been randomized (mean PD duration 5.7 years, range 1-14). MP powder is delivered every month and it is easy to use by patients. Some patients with longstanding disease showed a remarkable improvement in severe postural instability and dysphagia induced by MP (Video). Two PD patients are successfully cultivating Mucuna plant in their own garden (Fig.1A). MP seeds were planted in a hospital's garden (Fig.1B). Concerning safety, MP has an overall good tolerability. A few patients reported a progressive shortening of the ON-time after a few weeks of MP therapy.

Conclusion: If proven effective and tolerable, MP powder may be used as an alternative source of levodopa in the long-term for indigent PD patients worldwide.

FIG. 1 (LBA 16)

LBA 17

Longitudinal, diffusion MRI-based white matter changes are associated with cognitive decline in early Parkinson's disease with comorbid Alzheimer's disease pathology from PPMI

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Objective: To determine if longitudinal changes in diffusion MRI of white matter (WM) are associated with changes in cognition over four years in Parkinson's disease (PD) participants from the Parkinson's Progression Markers Initiative (PPMI) study including just the subgroup with comorbid Alzheimer's disease (AD) pathology.

Background: Previous cross-sectional diffusion MRI studies have found diffusion tensor imaging (DTI) of WM to be associated with mild cognitive impairment and dementia in PD.1-5 It is well established that the subgroup of PD with comorbid AD pathology, reflected by low CSF ABeta 1-42 levels, experiences more rapid cognitive decline.6 Recently, we reported the novel finding of longitudinal increases in free-water (FW) corrected mean diffusivity (MD) in temporal lobe WM to be significantly associated with long-term cognitive decline in a small, single site PD cohort with a mean disease duration of 7 years.7 We sought to extend these preliminary findings in an earlier, larger, multi-site PD cohort using PPMI data.

Method: A total of 60 PD patients from PPMI were analyzed (downloaded April 2018). Patients were included if they had valid DTI data, Montreal Cognitive Assessment (MoCA), Symbol-Digit Modalities Test (SDMT) and Letter-Number Sequencing (LNS) scores at baseline and year 4 and also had CSF ABeta 1-42 assessments at baseline (from the 2016/2017 batch run). These cognitive assessments were chosen a priori based on previous results showing sensitivity to change.6 PD patients were split into two subgroups: those with CSF ABeta 1-42 500pg/ml (n =55) at baseline.8 Standard preprocessing of DTI data was performed. The diffusion tensor was calculated using both single tensor and bi-tensor models, with the later providing an estimate of free-water (FW) and FW-corrected MD and fractional anisotropy (FA) measures.9 Voxelwise analysis of the DTI data was performed using Tract-Based Spatial Statistics (TBSS).10 Associations between changes in WM DTI and cognitive measures over the four year period were assessed for the whole PD group, and interaction effects were assessed for the two subgroups.

Results: There were no significant differences in terms of age, sex, education or disease duration (8 vs. 7 months) between the two subgroups at baseline. There were no significant associations between changes in MoCA, SDMT or LNS and any of the DTI parameters in the whole PD group. However, there was a significant interaction with group status for several of the associations indicative of stronger associations in the low vs. high baseline CSF ABeta 1-42 subgroups (Table 1).

Conclusion: White matter DTI and FW, particularly in the corpus callosum body, may represent cognition progression biomarkers in early PD patients with comorbid AD pathology.

References: 1. Deng B, Zhang Y, Wang L, Peng K, Han L, Nie K, Yang H, Zhang L, Wang J. Diffusion tensor imaging reveals white matter changes associated with cognitive status in patients with Parkinson's disease. Am J Alzheimers Dis Other Demen 2013; 28:154-164. 2. Duncan GW, Firbank MJ, Yarnall AJ, Khoo TK, Brooks DJ, Barker RA, Burn DJ, O'Brien JT. Gray and white matter imaging: A biomarker for cognitive impairment in early Parkinson's disease? Mov Disord 2016; 31:103-110. 3. Melzer TR, Watts R, MacAskill MR, Pitcher TL, Livingston L, Keenan RJ, Dalrymple-Alford JC, Anderson TJ. White matter microstructure deteriorates across cognitive stages in Parkinson disease. Neurology 2013; 80:1841-1849. 4. Hattori T, Orimo S, Aoki S, Ito K, Abe O, Amano A, Sato R, Sakai K, Mizusawa H. Cognitive status correlates with white matter alteration in Parkinson's disease. Hum Brain Mapp 2012; 33:727-739. 5. Agosta F, Canu E, Stefanova E, Sarro L, Tomic A, Spica V, Comi G, Kostic VS, Filippi M. Mild cognitive impairment in Parkinson's disease is associated with a distributed pattern of brain white matter damage. Hum Brain Mapp 2014; 35:1921-1929. 6. Caspell-Garcia C, Simuni T, Tosun-Turgut D, Wu IW, Zhang Y, Nalls M, Singleton A, Shaw LA, Kang JH, Trojanowski JQ, Siderowf A, Coffey C, Lasch S, Aarsland D, Burn D, Chahine LM, Espay AJ, Foster ED, Hawkins KA, Litvan I, Richard I, Weintraub D, Parkinson's Progression Markers I. Multiple modality biomarker prediction of cognitive impairment in prospectively followed de novo Parkinson disease. PLoS One 2017; 12:e0175674. 7. Guttuso T, Jr., Bergsland N, Hagemeier J, Lichter DG, Pasternak O, Zivadinov R. Substantia Nigra Free Water Increases Longitudinally in Parkinson Disease. AJNR Am J Neuroradiol 2018. 8. Compta Y, Buongiorno M, Bargallo N, Valldeoriola F, Munoz E, Tolosa E, Rios J, Camara A, Fernandez M, Marti MJ. White matter hyperintensities, cerebrospinal amyloid-beta and dementia in Parkinson's disease. J Neurol Sci 2016; 367:284-290. 9. Pasternak O, Sochen N, Gur Y, Intrator N, Assaf Y. Free water elimination and mapping from diffusion MRI. Magn Reson Med 2009; 62:717-730. 10. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 2006; 31:1487-1505.

TABLE 1 (LBA 17)

Table 1: Lithium concentrations in materials of interest

Material	Lithium Concentration (µg/gm)
Camel Blue cigarette	24.98
Camel Turkish Gold cigarette	15.00
Marlboro Red cigarette	15.08
Marlboro Gold cigarette	12.58
American Spirit cigarette	2.58
Seneca 100 cigarette	9.52
Izmir Turkish Oriental Tobacco	65.54
Samsun Turkish Oriental Tobacco	53.06
Brightleaf Virginia Tobacco	11.07
American Virginia Tobacco	0.00
Indian Tobacco (Jathar et al. 1980)	12.0
Red Bell Pepper	0.20
Orange Bell Pepper	0.21
Green Bell Pepper	0.16
Yellow Bell Pepper	0.10
Tasters Choice Instant Regular Coffee	0.004
Tasters Choice Instant Decaffeinated Coffee	0.004

LBA 18

Self-Help and education using the Internet for Functional Motor Disorders (SHIFT) - A Randomised Controlled Trial

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Objective: In this randomised trial we aimed to investigate if an online education and self-help intervention, added to usual care, would improve self-rated health at six months and secondary outcomes at three and six months, in functional motor disorders (FMD).

Background: The treatment approach of functional motor disorders has been heterogeneous and poorly studied for many years, while the disorder is often chronic and impairing. Recently, a stepped care approach has been suggested, in which explanation of the diagnosis is the first step.

Method: Patients were randomised into a group with access to the newly developed online intervention on top of usual care, or a group with usual care only. Patients from 31 centers in the Netherlands that were >17 years of age and had a functional motor symptom which caused distress or impairment were included. The primary outcome was self-rated health on the Clinical Global Improvement (CGI) scale, at 6 months follow-up. Secondly, we measured severity of motor symptoms, other physical and psychiatric symptoms, illness beliefs, satisfaction with treatment and with the website intervention, referral to physiotherapy and psychotherapy, health related quality of life and functioning and work and social adjustment at three and six months. Nonparametric statistics on between x within comparisons in both intention to treat and planned post hoc per protocol analysis were used.

Results: 186 patients were randomised. Follow-up rate at 6 months was 90% in the intervention group and 85% in the control group for the primary outcome. 68% of patients in the intervention group visited the online intervention. There was no statistical difference in the number of patients that improved on the primary outcome (self-rated health) at 6 months in the intention to treat analysis (42% vs 46% after imputation). Per protocol analysis showed no positive effect (p=0.727), nor harm (p=0.099). In the intention

to treat analysis, most secondary outcomes did not differ between groups, trust in the diagnosis was higher in the intervention group (median 4 (IQR2) vs 3 (1), p=0.014) at three months, but not at six months. Satisfaction with the intervention was high, 84% of patients would recommend it to other patients and 62% stated the website helped them a lot at six months.

Conclusion: In this study, we found no significant effect of an education and self-help online intervention added to usual care compared to usual care only, on self-rated health in patients with FMD. It was shown no harm was done with the intervention. Although no significant improvement was found on most secondary outcome measures in the intervention group versus the control group, large patient satisfaction with the intervention was reported. These results suggest education and self-help could still be very valuable in the stepped care of FMD, but might not be effective as a single intervention. More research is needed to determine which patients might benefit from education and self-help specifically.

LBA 19

Variation at the TRIM11 locus modifies Progressive Supranuclear Palsy phenotype

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Objective: The basis for clinical variation related to underlying Progressive Supranuclear Palsy (PSP) pathology is unknown. We performed a genome wide association study (GWAS) to identify genetic determinants of PSP phenotype.

Background: Richardson's syndrome (RS) is the most common clinical phenotype related to PSP pathology. In recent years, we and others have identified alternative clinical phenotypes related to PSP pathology in relatively small case series, such as PSP-Parkinsonism (PSP-P) and Pure Akinesia with Gait Freezing (PAGF). PSP-P and PAGF have been shown to have a similar age of disease onset to RS, clinically resemble RS in the latter stages of disease, but have a significantly longer mean disease duration.

Method: Two independent pathological and clinically diagnosed PSP cohorts were genotyped and phenotyped to create Richardson's syndrome (RS) and non-RS (PSP-P and PAGF combined) groups. We carried out separate logistic regression GWAS to compare RS and non-RS groups and then combined datasets to carry out a whole cohort analysis (n=497). We validated our findings in a third cohort by referring to data from 100 deeply phenotyped cases from the original PSP case-control GWAS. We assessed the expression/co-expression patterns of our identified genes and used our data to carry out gene-based association testing.

Results: Our lead single nucleotide polymorphism (SNP), rs564309, showed an association signal in both cohorts, reaching genome wide significance in our whole cohort analysis – OR 5.55, p-value $1.7x10^{-9}$ (Figure 1)(Table 1). rs564309 is an intronic variant of the tripartite motif-containing protein 11 (TRIM11) gene (Figure 2), a component of the ubiquitin proteasome system (UPS). In our third cohort, minor allele frequencies of surrogate SNPs in high linkage disequilibrium with rs564309 replicated our findings. Gene based association testing confirmed an association signal at TRIM11. We found that TRIM11 is predominantly expressed in neurons of the cerebellum and basal ganglia.

Conclusion: Our study suggests that the TRIM11 locus is a genetic modifier of PSP phenotype and potentially adds further evidence for the UPS having a key role in tau pathology, therefore representing a target for disease modifying therapies.

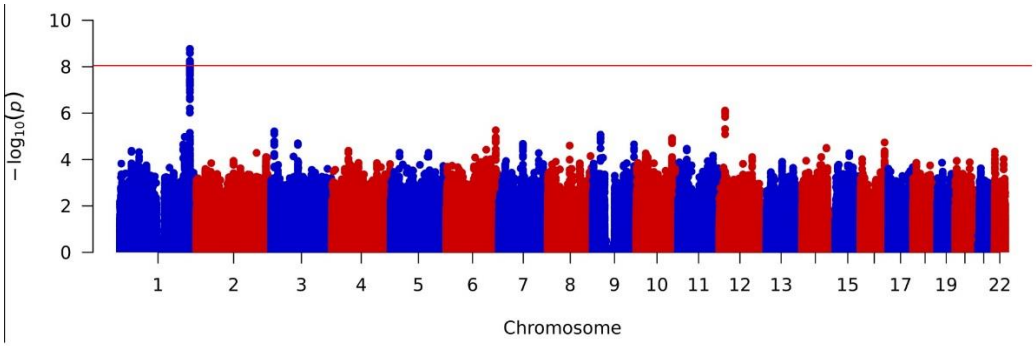

FIG. 1 (LBA 19)

TABLE 1 (LBA 19)

Chr. band	SNP Position (BP)	Gene	MAF in healthy controls	Pathological cohort				Clinical cohort				Whole cohort	
				MAF in RS	MAF in non-RS	OR (95% CI)	P_1	MAF in RS	MAF in non-RS	OR (95% CI)	P_2	OR (95% CI)	P_x
1q42.13	rs564309 228,585,562	TRIM11	0.10	0.04	0.19	6.25 (3.12-12.5)	$4.1x10^{-7}$	0.04	0.16	4.76 (1.96-12.5)	$7.5x10^{-4}$	5.55 (3.22-10.0)	$1.7x10^{-9}$
	rs61827276 228,597,130	TRIM17	0.09	0.04	0.18	5.88 (2.78-12.5)	$2.3x10^{-6}$	0.04	0.16	5.55 (2.17-14.3)	$4.1x10^{-4}$	5.55 (3.12-10.0)	$6.2x10^{-9}$
	rs61825312 228,530,748	OBSCN	0.10	0.04	0.19	5.88 (2.86-12.5)	$1.3x10^{-6}$	0.04	0.16	4.35 (1.78-11.1)	$1.3x10^{-3}$	5.26 (2.94-9.09)	$7.1x10^{-9}$
	rs2230656 228,612,838	HIST3H3	0.11	0.06	0.23	4.35 (2.32 -8.33)	$3.5x10^{-6}$	0.06	0.20	3.70 (1.75-8.33)	$7.4x10^{-4}$	4.00 (2.50-6.67)	$1.3x10^{-8}$

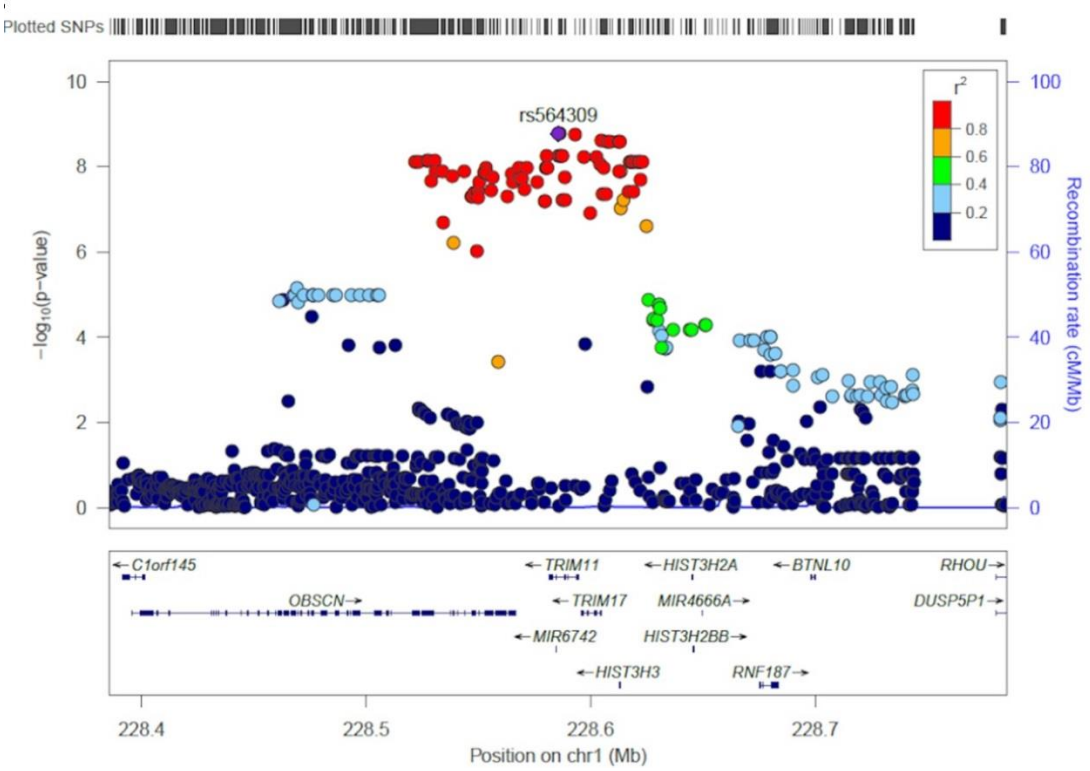

FIG. 2 (LBA 19)

LBA 20

Metabolic profiling reveals new serum biomarkers of spinocerebellar ataxia 3

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Objective: The objective of this study is to explore the systematic metabolic disturbance and potential peripheral biomarkers in preclinical and manifest spinocerebellar ataxia 3 (SCA3) patients.

Background: Spinocerebellar ataxia 3/Machado-Joseph disease (SCA3/MJD) is the most common spinocerebellar ataxias. The pathogenesis mechanisms are not fully elucidated and no therapeutic approach can alleviate the symptoms effectively. Some disease-modifying compounds have been emerging in the clinical trials, while sensitive methods to measure the subtle therapeutic benefits are still absent. Therefore, noninvasive peripheral biomarkers are greatly needed to anticipate onset of disease, monitor disease progression, identify prospective drug targets, assess therapeutic effect, and uncover potentially pathogenic mechanisms.

Method: A cohort of 26 genetically confirmed SCA3 patients were enrolled, including 13 preclinical SCA3 patients and 13 manifest SCA3 patients. Meanwhile, 15 age, sex, and BMI-matched healthy volunteers were enrolled as controls. Metabolic profiling of serum samples was mapped using ultrahigh-performance liquid chromatography-mass spectrometry (UPLC-MS) and gas chromatography-mass spectrometry (GC-MS). Multivariate analysis was performed using SIMCA P+ 13.0 software. Metabolites with VIP > 1.0 were chosen for Wilcoxon−Mann−Whitney test by SPSS software. Metabolites with both multivariate significance and univariate significance (VIP > 1.0 and $p < 0.05$) were considered as the differential markers. Receiver operating characteristic curve (ROC) analysis and Logistic regression analysis were performed to evaluate the predictive potential of the candidate biomarkers.

Results: Totally, 321 known metabolites were clearly identified. From the PCA score plot, manifest SCA3 group were separated significantly from control and preclinical SCA3 group, while preclinical SCA3 group and control group were overlapped (R2Xcum = 0.93, Q2cum = 0.86). The R2Ycum and Q2Ycum of the OPLS-DA model for manifest SCA3 group and control group were 0.945, 0.794. The R2Ycum and Q2Ycum of the OPLS-DA model for SCA3 group and preclinical SCA3 group were 0.851, 0.691. In total, 18 differential metabolites were highlighted between groups, including MUFA, SFA, PUFA, FFA 16:0, FFA 16:1, FFA 18:1, FFA 18:2, FFA 18:3, GCDCA, Valine, Leucine, Tryptophan, Tyrosine, Phenylalanine, Proline, Acetylcarnitine, Hippuric acid. Metabolites with area under the curve (AUC) > 0.7 of ROC curve were selected as potential biomarkers. FFA16:1, FFA18:3, proline and tryptophan were selected as potential biomarkers. The combined diagnostic ROC with FFA16:1, FFA18:3, proline and tryptophan by binary logistic analysis were also performed, with AUC reached 0.979.

Conclusion: The serum metabolic profiling was altered with the progress of the disease in SCA3 patients, mainly associated with amino acid metabolism and fatty acid metabolism pathways. A panel of four potential biomarkers, including FFA16:1, FFA18:3, proline and tryptophan, is proposed to disease biomarkers, which providing a novel and promising diagnostic approach for detection of SCA3.

LBA 21

Safety, tolerability and pharmacokinetics of oral venglustat in Parkinson's disease patients with a GBA mutation

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Objective: Assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of oral venglustat, a CNS-penetrating glucosylceramide (GL-1) synthase inhibitor, in Parkinson's disease (PD) patients with a GBA mutation.

Background: Mutations in GBA, which encodes glucocerebrosidase, are associated with increased risk of developing PD, characterized by a younger onset, higher prevalence of cognitive impairment, and more rapid disease progression.

Methods: Part 1 of the phase 2 MOVES-PD study (NCT02906020) was a 36-week randomized, placebo-controlled, double-blind, sequential cohort study of venglustat at 3 escalating doses. PD patients age 18-80 years with symptoms ≥2 years and Hoehn & Yahr stage ≤2 at baseline who were heterozygous carriers of a GBA mutation were eligible. The primary endpoint of Part 1 was the safety and tolerability of venglustat. Secondary endpoints included plasma and cerebrospinal fluid (CSF) PK. Exploratory endpoints included pharmacodynamics in plasma and CSF.

Results: Seventeen patients (13M, 4F) were enrolled and randomized to placebo (n=4) or venglustat (n=13). Mean age (SD) at enrollment was 58.4 (7.9) years. Mean (SD) years since symptom onset was 6.7 (4.0), and since diagnosis was 5.2 (4.4). Twelve patients on venglustat and 4 on placebo reported at least 1 treatment emergent adverse event (TEAE); most were mild or moderate and resolved without corrective treatment during the study. The most common TEAEs were psychiatric, neurological, and gastrointestinal events consistent with common motor/non-motor PD symptoms or known side effects of concurrent PD medications. No serious AEs or deaths occurred. Two patients on venglustat discontinued due to TEAEs after the primary analysis period (Week 4). Venglustat exposure in plasma and CSF increased in a close to dose proportional manner. Plasma and CSF GL-1 levels decreased from MDS 2018_MOVES-PD Part 1 Abstract Submission 2 baseline in a dose-dependent manner over 4 weeks of treatment. CSF GL-1 decreased 74.3% (higher dose arm).

Conclusion: The data demonstrate a favorable safety and tolerability profile of venglustat at all doses investigated for up to 36 weeks of treatment, allowing progression to Part 2. Dose-dependent plasma and CSF exposure and reduction of plasma and CSF GL-1 were observed. Part 2 of MOVES-PD, a 52-week randomized, double-blind, placebo-controlled 2-arm study, is ongoing.

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LBA 22

Proof-of-Concept, Double-Blind, Placebo-Controlled Study for CX-8998 a State-Dependent T-Type Calcium (Cav3) Channel Antagonist in Essential Tremor Patients (T-CALM): Efficacy and Safety Results

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Objective: To determine the efficacy, safety, tolerability and plasma concentrations of CX-8998 in patients with essential tremor (ET) with inadequate response to standard of care anti-tremor medications.

Introduction: ET is among the most prevalent of movement disorders in adults. Propranolol is the only medication approved for the treatment of ET. The T-type calcium channel, Cav3, is a mediator of subthreshold oscillations and excessive rhythmicity in pathophysiologic states found in tremor and is highly expressed in functional tremor network regions. Tremor-related oscillations are a neuronal signature for ET and Cav3 plays a critical role in their generation. CX-8998 is a potent, selective, and state-dependent small molecule blocker of Cav3 channels.

Methods: We recently completed a randomized, double-blind, placebo-controlled, parallel-group study (NCT03101241) of 95 patients with ET that have an inadequate response to anti-tremor medication (e.g., propranolol). Following consent and screening, subjects were randomized to receive oral doses of either CX-

8998 (titrated up to 10mg BID) or placebo for 28 days. Clinical rating scales, patient-reported outcomes and accelerometer recordings of tremor and digital spirography were collected at baseline (visit 1), day 15 (visit 3) and day 28 (visit 4).

Results: Investigator-rated TETRAS (The Essential Tremor Rating Assessment Scale) Performance Subscale (p=0.027), TETRAS ADL (p=0.049), TETRAS total score (p=0.007) and Clinician Global Impression of Improvement (p=0.001) significantly improved. Centrally-rated TETRAS Performance Subscale (primary endpoint) did not reach significance. There were no major safety and tolerability concerns.

Conclusion: The study achieved proof-of-concept in ET and identified key pivotal study design parameters including primary and secondary efficacy endpoints, patient population and titration scheme. CX-8998 was safe and well tolerated in ET patients. Further studies are needed to evaluate the efficacy of CX-8998 in ET patients. These results are expected to enable late-stage development of CX-8998 in ET.

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