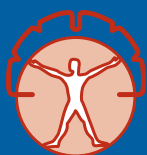# Late-Breaking Abstracts

International Parkinson and Movement Disorder Society

International Congress of Parkinson's Disease and Movement Disorders®

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International Congress of Parkinson's Disease and Movement Disorders® 2019 Late-Breaking Abstracts

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LBA 1

Knowledge and attitudes regarding genetic testing for Parkinson's disease among US and Canadian Parkinson's disease specialists

R. Alcalay, C. Kehow, R. Battista, A. Hall, T. Simuni, K. Marder, A. Wills, A. Naito, J. Beck, M. Schwarzschild, M. Nance (New York, NY, USA)

Objective: To assess movement disorders specialists' knowledge, attitudes and perceived barriers to genetic counseling and testing in PD.

Background: Our awareness of the genetic contribution to Parkinson's disease (PD) has expanded in recent years, and clinical trials of treatments specific to carriers of certain variants in LRRK2 and GBA have begun. In the past, genetic testing for PD has not been widely used in clinical practice, but to keep pace with therapeutic developments, we need to develop clinical and logistical approaches to genetic testing and counseling for this etiologically complex disease.

Method: An anonymous questionnaire was sent to clinician-members of the Parkinson Study Group (PSG), comprising movement disorders specialist at some 140 clinical sites in Canada and the US, to assess knowledge their knowledge and attitudes about genetic testing in PD.

Results: 374 PSG clinicians were contacted; 178 questionnaires were returned. Forty-one percent of respondents did not refer any PD patients for genetic testing in the last year; 5% had referred 30 or more patients. About 25% of clinicians have access to genetic counseling within their neurology clinic, and two thirds had access to genetic counseling services within their institution. Only 4% had used remote (telephonic) genetic counseling services. Common reasons for not performing genetic testing included lack of insurance coverage/cost to the patient, lack of perceived utility of genetic information in clinical practice, and concerns about how genetic information could be used by third parties such as insurance or pharmaceutical companies. On a scale from 0-100, the mean level of comfort in counseling PD patients on GBA and LRRK2 was 52 (SD=28). Only 60% of clinicians answered questions about the inheritance and penetrance of GBA and LRRK2 variants correctly. The rest did not reply (20%), responded they were unsure (10%) or provided the wrong answer (10%).

Conclusion: As we learn more about the genetic contributions to PD, and begin trials of gene-specific treatments for GBA and LRRK2 mutation carriers, there is an urgent need to understand and reduce the knowledge, attitudinal, and practical barriers to genetic counseling and testing. Educating movement disorders clinicians about the analytic and clinical validity and utility of gene tests, disseminating expert recommendations for genetic testing in PD, and including genetic counselors as part of the multidisciplinary team in movement disorders clinics, are all potentially useful approaches.

LBA 2

Tau PET in Progressive Supranuclear Palsy. Multi-Center Evaluation of [18F]PI-2620

M. Brendel, T. van Eimeren, H. Barthel, K. Marek, M.T. Barbe, P. Bartenstein, L. Beyer, J. Classen, J. Hammes, J. Herms, J. Levin, B. Neumaier, M. Patt, S. Roeber, J.J. Rumpf, M. Rullmann, D. Russell, A. Stephens, V.L. Villemagne, G. Hoeglinger, A. Drzezga, J. Seibyl, O. Sabri, (Munich, Germany)

Objective: Multicenter-evaluation of the tau-binding tracer 18F-PI2620 in clinically diagnosed PSP Richardson syndrome (PSP-RS).

Background: Definite diagnosis of the 4R-tauopathy progressive supranuclear palsy (PSP) is currently only possible post-mortem. Interventional trials against tau would benefit from biomarkers validating target presence. First-generation tau-PET ligands showed relevant limitations, e.g., off-target binding potentially related to monoamine-oxidase (MAO). The second-generation tau-PET ligand 18F-PI2620 proved absent off-target binding to MAO and high affinity to 3/4R tau in Alzheimer's disease (AD).

Method: Twenty patients (71±6y, n=10 female) with probable or possible PSP-RS according to the MDS criteria (PSP rating scale: 38±17; range 13-71) together with ten matched healthy controls (HCs) and ten disease controls (multi-system atrophy, Parkinson's disease, Alzheimer's disease) underwent [18F]PI-2620 PET at five different centers. Multilinear reference tissue modelling with cerebellar reference served for calculation of 0-60min p.i. distribution volume ratios (DVRs). DVRs in PSP target regions (globus pallidus, substantia nigra, subthalamic nucleus, dentate nucleus) were compared between PSP-RS, HCs, and disease controls, and controlled for no-interest effects (center, age, sex). Additionally, globus pallidum tissue of PSP patients and HC was subjected to [18F]PI-2620 in vitro autoradiography (with/without blocking with 10μM 19F-PI2620).

Results: When compared to the HCs, elevated DVRs were observed in PSP-RS patients in the globus pallidus (1.17±0.09 vs. 1.00±0.06; p0.9). Even in PSP-RS patients with low disease severity (PSP rating scale ≤30; n=6), globus pallidus DVRs were significantly higher compared to the HCs (1.19±0.07 vs. 1.00±0.06; p=0.004). In vitro autoradiography showed displaceable tracer binding in the globus pallidus of PSP patients, but not in HCs.

Conclusion: Our multi-center data indicate the potential of dynamic [18F]PI-2620 PET imaging for early and pathology-specific diagnosis in PSP. Further studies, including more patients, earlier disease states (e.g. prodromal PSP) in both PSP-RS and other PSP variants are clearly warranted.
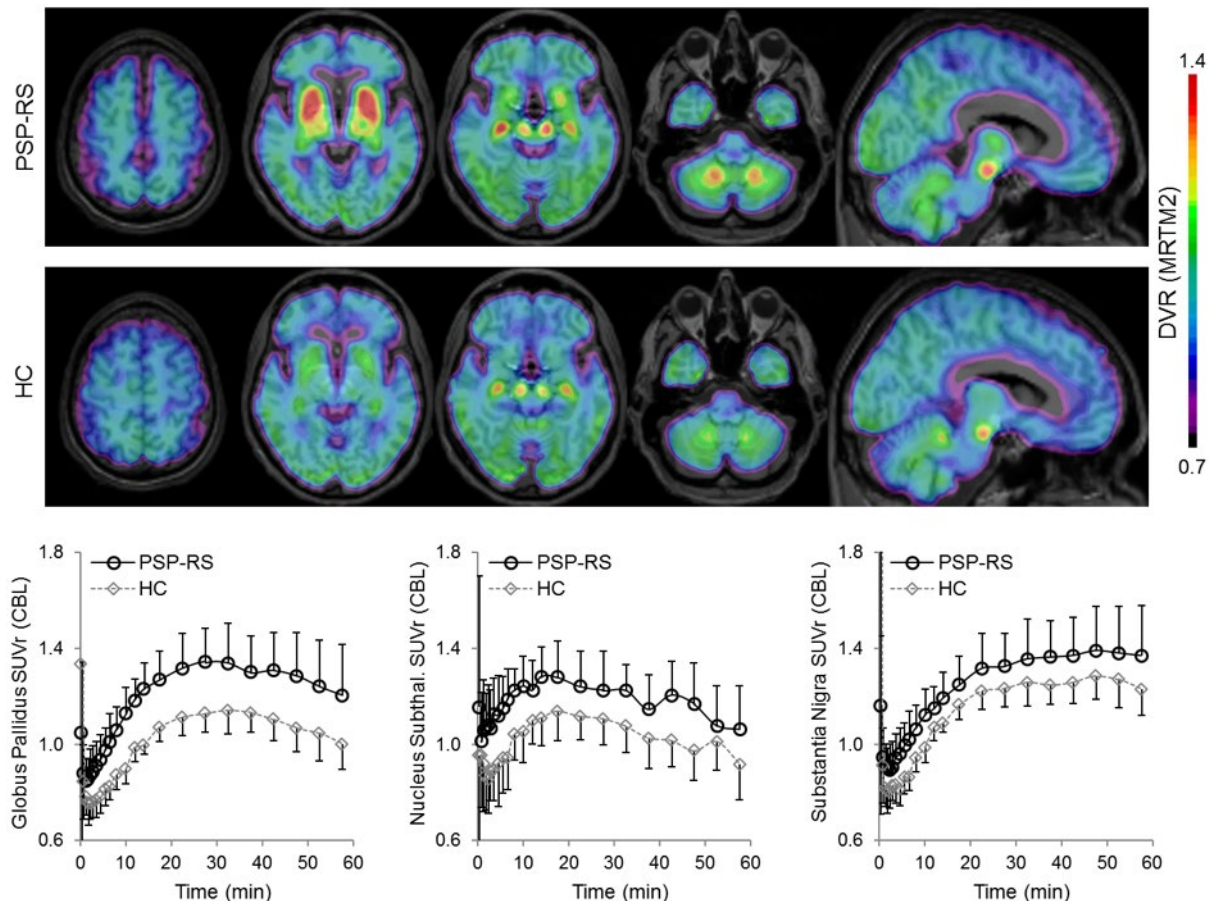

Figure 1

LBA 3
A randomised, placebo-controlled, first-in-human study with a central Tau epitope antibody – UCB0107

T. Buchanan, S. De Bruyn, T. Fadini, S. Watanabe, M. Germani, A. Boyden, I. Rebollo Mesa, G. Meno-Tetang, S. Zanigni, A. Colson, O. Famodimu, C. Ewen (Braine-l'Alleud, Belgium)

Objective: In vitro and in vivo studies show that the choice of epitope determines efficacy of therapeutic anti-Tau antibodies. Here, we report the safety, tolerability and PK of our anti-Tau antibody UCB0107, which targets a central Tau epitope.

Background: In tauopathies, it is hypothesised that the spread of Tau protein from neuron to neuron underpins disease progression. UCB0107 is a recombinant, humanised, full-length IgG4 anti-Tau antibody, developed to block/reduce the spread of Tau pathology.

Method: This was a first-in-human (FIH), randomised, double-blind, placebo (PBO)- controlled, single-ascending-dose study (NCT03464227). Healthy male adults were assigned to one of seven cohorts (C) and randomised 1:1 (C1) or 3:1 (C2–7) to receive UCB0107 or PBO by iv infusion. Primary endpoint:

incidence of AEs. Other safety assessments included: neurological examination, MRI, ECG, clinical chemistry, haematology, coagulation, urinalysis and vital signs. Additional secondary endpoints: serum and cerebrospinal fluid (CSF) PK parameters. CSF was collected for analysis (C3–7 only) at screening and on Days 7, 28 and 84.

Results: 52 participants (mean age 49.7 yrs) were randomised (UCB0107 C1 [n=2], C2–7 [n=6 each]); PBO (n=14); all completed the study. TEAEs are in Table 1 [table1]; the most common TEAE in the total UCB0107 and PBO groups was headache (n=6 participants [15.8%]; n=5 participants [35.7%], respectively). One severe TEAE of leg varicose ulceration was reported (Day 46; C7) in one participant with a history of varicose veins and varicose-vein stripping. No TEAEs were serious or drug related. There were no clinically relevant changes in other safety results. Serum and CSF concentrations increased with dose. CSF/serum ratio was constant across doses, maintained to Day 84. Safety and PK profiles suggested no anti-drug-antibody effect.

Conclusion: In this FIH study, UCB0107 was well tolerated with an acceptable safety profile after single-ascending dose administration by iv infusion. Serum and CSF concentrations increased with UCB0107 dose. This FIH study supports the progression of the clinical development of UCB0107 in patients with tauopathies, such as progressive supranuclear palsy.

UCB0107, UP0047, MDS 2019_final draft_22May2019

Table 1. Overview of TEAEs (FAS)

Category	Placebo (n=14) n (%) [#]	UCB0107 C1 (n=2) n (%) [#]	UCB0107 C2 (n=6) n (%) [#]	UCB0107 C3 (n=6) n (%) [#]	UCB0107 C4 (n=6) n (%) [#]	UCB0107 C5 (n=6) n (%) [#]	UCB0107 C6 (n=6) n (%) [#]	UCB0107 C7 (n=6) n (%) [#]	Total UCB0107 (n=38) n (%) [#]
Any TEAEs	9 (64.3) [14]	1 (50.0) [1]	0	6 (100) [14]	6 (100) [7]	4 (66.7) [5]	3 (50.0) [9]	5 (83.3) [11]	25 (65.8) [47]
Serious TEAEs	0	0	0	0	0	0	0	0	0
Discontinuations due to TEAEs	0	0	0	0	0	0	0	0	0
Drug-related TEAEs	0	0	0	0	0	0	0	0	0
Severe TEAEs	0	0	0	0	0	0	0	1 (16.7) [1]	1 (2.6) [1]
AEs leading to death	0	0	0	0	0	0	0	0	0
TEAEs leading to death	0	0	0	0	0	0	0	0	0

Note: n was the number of study participants reporting at least 1 TEAE in that category. Percentages were based on the total N
Note: [#] was the number of individual occurrences of the TEAE in that category. No TEAEs were considered drug related per investigator assessment.
AE, adverse event; FAS, Full Analysis Set; TEAE, treatment-emergent adverse event

LBA 4

Expiratory muscle strength training (EMST) for treatment of pharyngeal dysphagia in Parkinson's disease: A randomized controlled trial

I. Claus, P. Muhle, J. Suttrup, J. Schroeder, S. Suntrup-Krueger, R. Dziewas, T. Warnecke, (Muenster, Germany)

Objective: The purpose of this randomized, double-blind sham-controlled trial was to verify if a 4-week-expiratory muscle strength training (EMST) is able to improve pharyngeal dysphagia and particularly swallowing efficiency in the short and long term.

Background: Pharyngeal dysphagia in Parkinson's disease (PD) is a common and clinical relevant symptom associated with poor nutrition, reduced quality of life, and aspiration pneumonia. Despite this fact sufficient behavioral treatment approaches are rare.

Method: Fifty PD patients (f/m 9/41; age 67.2±8.2y; disease duration 6.6±3.4y; H&Y stadium 2.6±0.6) with hypokinetic pharyngeal dysphagia as confirmed by flexible endoscopic evaluation of swallowing (FEES) performed a 4-week EMST-training (5 days per week á 25 breaths per day). N=25 participants used a calibrated, n=25 a sham, handheld device. The primary outcome was a change in the Parkinson-specific endoscopic dysphagia severity scale. Secondary outcome measures were changes in FEES-subscales, SDQ and SWAL-QOL questionnaires. Swallowing function was evaluated directly before and after training period as well as after a period of 3 month using FEES. Swallowing-related cortical activation was measured in n=22 participants (real/sham: 11/11) via whole-head magnetencephalography (MEG).

Results: No pretreatment differences existed. Comparing FEES-scores before and after training period, the active group showed a relevant score improvement after 4 weeks (13.5 to 7.8 vs. 13.4 to 14.5 points;

Conclusion: The 4-week EMST-training significantly reduces overall dysphagia severity in PD patients with a sustained effect after three months compared to sham training. This was mainly achieved by improving pharyngeal hypokinesia and swallowing efficiency. The treatment effect on swallowing muscles is probably caused by peripheral mechanisms as no changes in the cortical swallowing network could be found.

LBA 5
Serum biomarkers of early untreated Parkinson's disease
P. Dusek, L. Kotackova, D. Springer, Z. Vanickova, M. Kalousova, T. Zima, H. Raszkova, R. Jech, K. Sonka, E. Ruzicka, F. Ruzicka (Prague, Czech Republic)

Objective: To find serum biomarkers of early untreated Parkinson's disease (PD).

Background: Finding serum biomarkers of neurodegenerative disorders is desirable as they are comparatively non-invasive and cheap. Several serum markers of PD were previously identified; however, mostly in advanced patients on dopaminergic treatment.

Method: 61 drug-naïve PD patients (age 59.9±12.9) and 51 healthy controls (age 63.6±8.6) were included. Their serum levels of following cytokines were determined immunochemically by biochip array (Randox Laboratories, UK) or enzyme-linked immunosorbent assay (ELISA; RD Systems, Minneapolis, USA; IBL International GMBH, Germany) kits: interleukin(IL)1a, IL1b, IL2, IL4, IL6, IL8, IL10, Interferon-gamma (IFNG), Tumor Necrosis Factor-alpha (TNFA), Monocyte Chemoattractant Protein-1 (MCP1), Epidermal Growth Factor (EGF), Vascular Endothelial Growth Factor (VEGF), Brain-Derived Neurotrophic Factor (BDNF), Soluble Receptor for Advanced Glycation End Products (sRAGE), High Mobility Group Box-1 (HMGB-1), Asymmetric dimethylarginine (ADMA), and Matrix Metalloproteinases-2 and 9 (MMP2/MMP9). Independent samples T-test was used for between-group comparison. For cytokines with significant differences Receiver Operating Characteristic (ROC) curve analysis was performed to determine the optimal cut-off score for differentiating PD and controls.

Results: PD patients had significantly lower serum levels of VEGF (p<0.05), EGF (p<0.05), and MMP9 (p<0.0001) compared to controls. ROC analysis showed optimal cut-off value for VEGF 41ng/ml (sensitivity/specificity 65/51%; AUC 0.63, CI95% 0.52-0.73); EGF 36ng/ml (sensitivity/specificity 65/51%; AUC 0.61, CI95% 0.50-0.72); and MMP9 496ng/ml (sensitivity/specificity 73/81%; AUC 0.78, CI95% 0.68-0.89).

Conclusion: Comparison of levels of various cytokines showed that angiogenesis-related molecules, VEGF, EGF, and MMP9 are down-regulated in serum of early stage drug-naïve PD patients. MMP9 may be used as a biomarker for PD with acceptable sensitivity and specificity.

LBA 6
Mapping of 1,633 goals from the tower study reveals a higher proportion of activity and participation-related goals in spasticity patients
K. Fheodoroff, A. Schesconka, J. Wissel, S. Ramusch (Hermagor, Austria)

Objective: In order to gain insight into areas of interest from the spasticity patient's perspective, we mapped the goals within the TOWER study using the International Classification of Functioning, Disability, and Health (ICF) categories and the EQ-5D domains.

Background: Goal setting is a significant challenge for individualized toxin treatment in patients with movement disorders. The ICF identifies and structures patient goals and may provide the expanded framework for treatment impact on individual task performance.

Method: A total of 1,633 individualized spasticity-related treatment goals collected according to the Goal Attainment Scale (GAS) during the TOWER study were mapped by following the ICF linking rules and the EQ-5D domains. Two researchers familiar with the ICF and ICF linking rules independently reviewed the goals. In the case of ambiguity, a third expert provided the final decision on the most appropriate linking. The degree of consensus and differences acts as a measure of comprehensibility of the goals. Goal categories are described according to the ICF framework.

Results: A high level of agreement in the main ICF concept (i.e., what the goal is about) was achieved (N=1570; 96.1%) and was dependent upon 3 factors: knowledge of ICF items, understandable goal statements, and appropriateness of linking rules. Eight hundred and ninety seven (54.9%) goals were task related (activity/participation). The main domains were problems with walking / mobility (N=318, 35.4%) undertaking single/multiple tasks (N=170; 18.9%) and dressing (N=112, 12.5%). Body functions were represented in 44% of patient goals: 21.4% related to pain and 44.7% related to muscle tone. Only 65% of goals were to be linked to the EQ-5D categories.

Conclusion: The results reveal a higher proportion of activity/participation-related goals including single/multiple tasks such as stretching, positioning and exercising. This analysis sheds new light on the patient need and also the perspectives of patient-centered goal-driven botulinum toxin treatment in spasticity. The ICF offers a broader framework for patient-centered goal setting and may increase comparability of clinical data. EQ-5D seems to miss more than 35% of goals that matter to patients with focal spasticity.

LBA 7
Effectiveness of a dance-physiotherapy combined treatment in minimizing the impact of motor and non-motor Parkinson's disease symptoms
E. Frisaldi, P. Bottino, M. Fabbri, M. Trucco, A. De Ceglia, N. Esposito, B. Diletta, E. Milano, G. Massazza, M. Zibetti, L. Lopiano, F. Benedetti (Turin, Italy)

Objective: Examine the effectiveness of a new dance-physiotherapy combined treatment (DArT method), which emphasize the teacher-patients interaction and avoid the aid of music, in minimizing motor and non-motor Parkinson's disease (PD) symptoms.

Background: Exercise has symptomatic benefits on PD and may slow down its progression. Dance has shown meaningful benefits for people living with PD, improving motor performance, mobility, quality of life, and adherence to physical activity over the long term.

Method: A Phase II, single blind, randomized, controlled pilot study was conducted on 24 mild-moderate PD patients, treated with Levodopa or dopamine agonists. The therapeutics consisted in an add-on protocol where the control group attended 30 hours of conventional physiotherapy, while the experimental group attended a dance-physiotherapy combined treatment including 15 hours of contemporary dance classes with ballet elements in addition to 15 hours of conventional physiotherapy. Before and after the training period (5 weeks), patients were assessed for 13 validated outcome measures describing motor, emotional, cognitive, and sensory components of PD, plus a final questionnaire specifically developed for the study (Cronbach's alpha=0.802).

Results: Key findings focused on the motor component assessed by MDS-UPDRS Part III scores. Both control and experimental groups showed comparable baseline MDS-UPDRS-III scores, even when patients were stratified according to disease severity (Table 1). Mild PD patients assigned to the experimental group showed significantly higher post treatment MDS-UPDRS-III scores compared to the related control group [8.167 (CI95%: 1.019 to 14.3159], with a large practical-clinical significant effect size (d=1.52) (Fig. 1). Accordingly, the final questionnaire revealed that mild PD patients of the experimental group expressed the higher satisfaction compared to the related control group (p=0.003, d= -2.76) (Fig. 2). Withdrawal and fall rates were equal to 0% for the whole sample.

Conclusion: Based on these preliminary findings, dance-physiotherapy combined treatment was very effective in minimizing the impact of motor symptoms in mild PD patients. Further studies are already underway to increase sample size, investigate non-motor PD symptoms in more detail, and assess additional outcome measures.

Table 1. Baseline characteristics

Measurement	Control group	Experimental group	P Value [a]
Whole sample size (N=24; 12 vs 12)			
Age, years	60.33 (7.82)	61.75 (7.06)	0.646
Duration from PD onset to the entry, years	6.54 (2.33)	7.04 (3.48)	0.683
Hoehn and Yahr, median (range)	2.00 (2.00–2.00)	2.00 (1.5-2.5)	1.000
MDS-UPRDS III (medication on)	19.00 (6.76)	18.83 (10.68)	0.964
Gender			0.653
Male, n (%)	9 (75)	8 (67)	
Female, n (%)	3 (25)	4 (33)	
BMI	26.17 (3.90)	26.08 (4.23)	0.817
LEDD (mg)	682.09 (198.07)	641.17 (358.40)	0.931
MoCA	25.50 (3.34)	26 (2.98)	0.599
Moderate PD patients (N=11; 6 vs 5)			
Age, years (SD)	62.17 (6.55)	61.60 (8.29)	0.902
Duration from PD onset to the entry, years	6.50 (1.87)	8.00 (4.36)	0.462
Median Hoehn and Yahr, median (range)	2.00 (2.00-2.00)	2.00 (1.5-2.00)	0.273
MDS-UPRDS III (medication on)	19.17 (4.79)	28.00 (10.70)*	0.101
Gender			0.621
Male, n (%)	4 (67)	4 (80)	
Female, n (%)	2 (33)	1 (20)	
BMI	26.88 (3.25)	24.42 (1.67)	0.162
LEDD (mg)	709.85 (113.83)	692.4 (328.16)	0.914
MoCA	25.50 (3.21)	26.8 (1.48)	0.428
Mild PD patients (N=13; 6 vs 7)			
Age, years	58.50 (9.14)	61.86 (6.74)	0.462
Duration from PD onset to the entry, years	6.58 (2.91)	6.36 (2.87)	0.890
Median Hoehn and Yahr, median (range)	2.00 (2.00-2.00)	2.00 (2.00-2.50)	0.355
MDS-UPRDS III (medication on)	18.83 (8.80)	12.29 (3.59)*	0.136
Gender			0.307
Male, n (%)	5 (83)	4 (57)	
Female, n (%)	1 (17)	3 (43)	
BMI	25.47 (4.66)	27.27 (5.20)	0.527
LEDD (mg)	654.33 (267.40)	604.57 (399.94)	0.801
MoCA	25.5 (3.782)	25.429 (3.735)	0.973

a. Two-sample t test was used for group comparison if the normality assumption had been satisfied; otherwise, the Mann Whitney test was used. The Chi-square test was used for group comparison in case of categorical variables (i.e. gender). * Two-sample t test showed a significant difference between the mean MDS-UPDRS III scores of the experimental groups of both first and second cycles (p = 0.004).

Figure 1. Post treatment MDS-UPDRS-III mean values and 95% CI
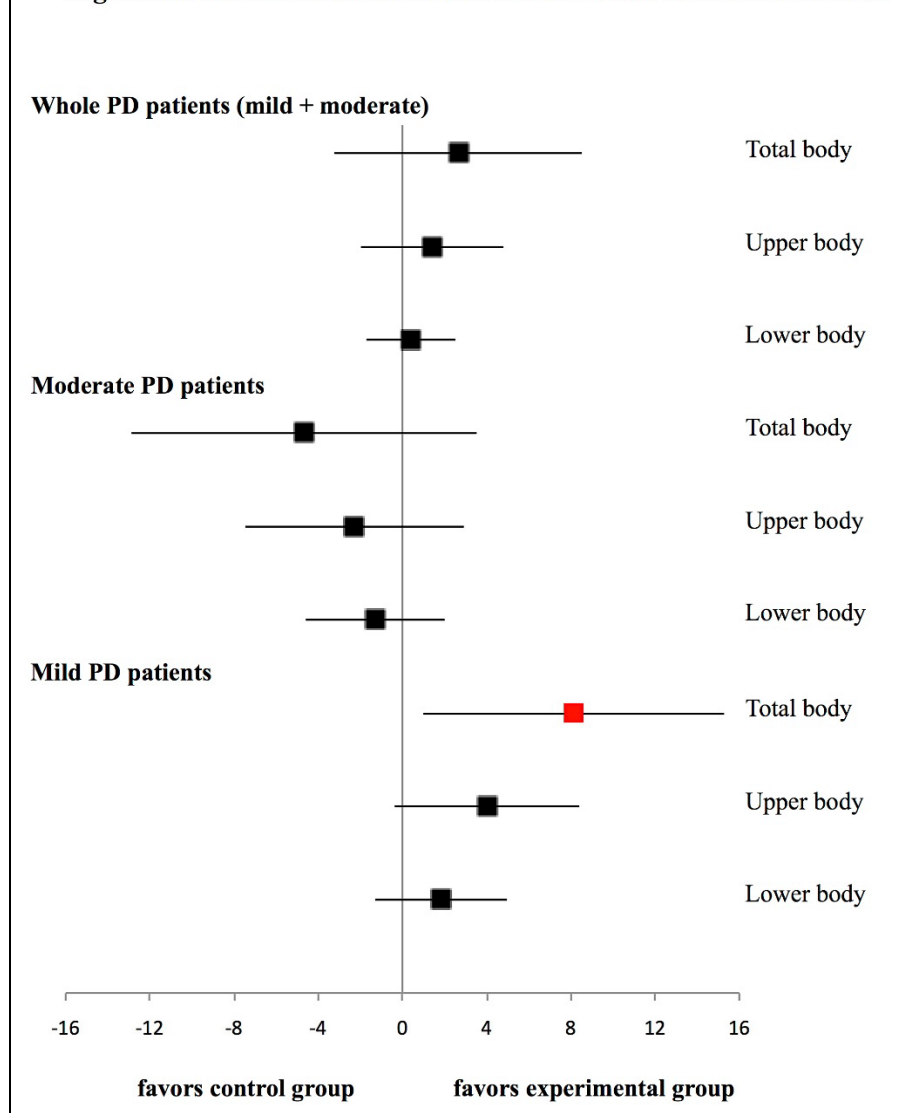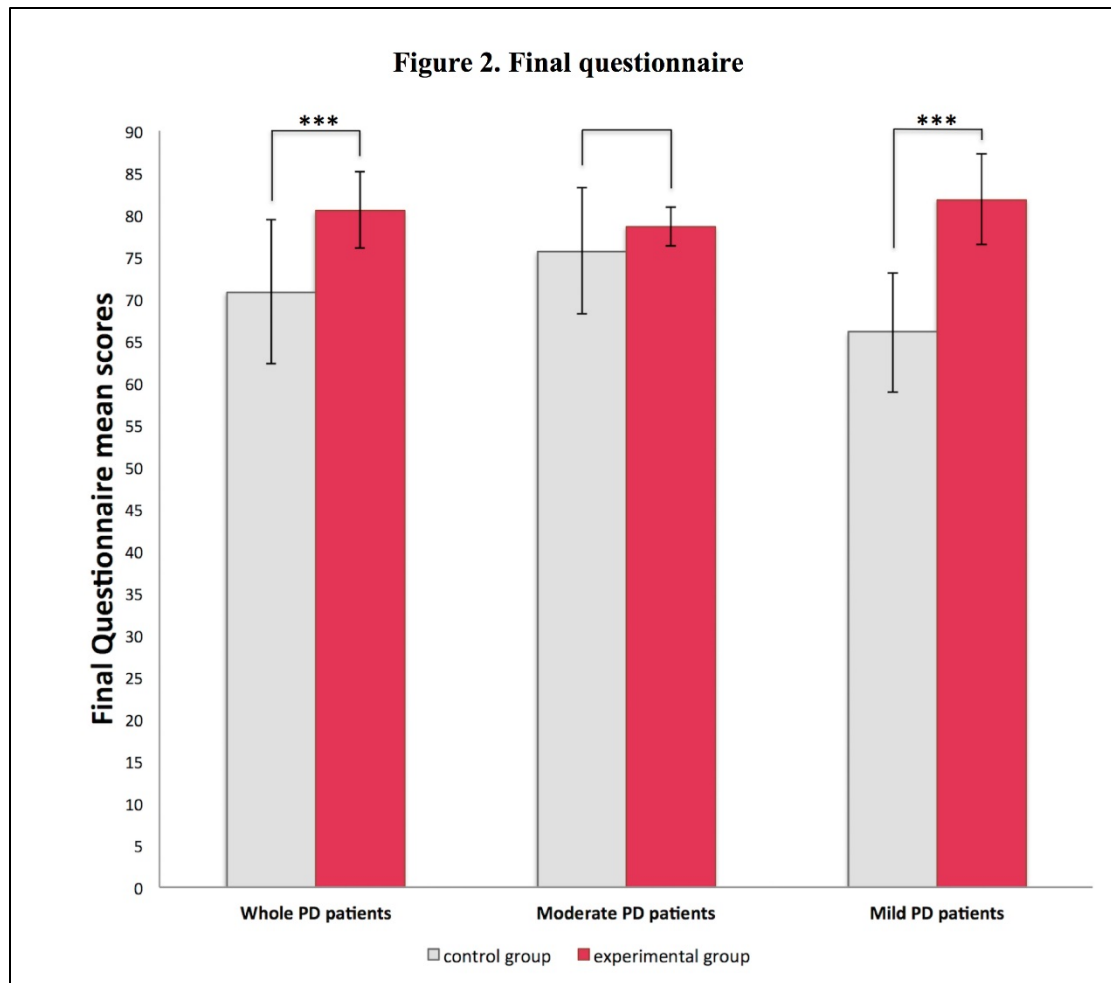
Figure 2. Final questionnaire

LBA 8
A Dose Ranging, Placebo-Controlled, 28-Day, Safety and Biomarker Phase 2a Study in GBA-PD Patients with the Selective GCase Activator, LTI-291
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Objective: A placebo-controlled, dose ranging, Phase 2a study in GBA-PD patients was conducted with the allosteric CNS penetrant GCase activator, LTI-291. The primary goals were safety, tolerability, and assessment of biomarker changes indicating GCase enzyme activation/target engagement.
Background: Heterozygote mutations in GBA1, encoding GCase, are the most common genetic risk factor for PD occurring in up to 15% of patients. Initial single and multiple ascending dose studies of LTI-291 in normal subjects showed the drug to be safe and well-tolerated, with excellent CNS penetration.
Method: 40 GBA-PD patients were enrolled and administered LTI-291 (at doses of 10, 30, 60mg/d) or placebo; (n=10/group) for 28 days. Key eligibility criteria required that patients were H&Y I-IV, MMSE> 18 and were on stable anti-PD medications for at least one month. Peripheral blood mononuclear cells (PBMCs) and plasma were analyzed for glycosphingolipid (GSL; 5 GluCer species, 7 LacCer species, and GluSph) changes at Days 6, 14 and 28. CSF was analyzed for GSL changes by comparing a Day 28 CSF sample to pre-dose CSF.
Results: There were no serious adverse events (SAEs) reported and the pattern of severity and types of AEs were the same in all the LTI-291 dose groups versus the placebo group. At all doses administered, statistically significant changes in a number of GluCer and LacCer species from peripheral PBMCs were

observed by analysis with ANOVA, ANCOVA, and a Responder Analysis compared to the effects observed in the placebo patients. The treatment effects observed in the 60 mg LTI-291 group was generally larger than in the other LTI-291 dose groups. GSL changes in GBA-PD patients with 'severe' mutations (mutations associated with Gaucher's disease; GD) were larger than in those with 'mild' mutations (ie those associated with PD but not with GD).

Conclusion: LTI-291 was safe and well tolerated over 28 days of dosing in GBA-PD patients. Significant changes in PBMC GSLs were observed, consistent with the drug having its intended biologic effect on GCase. The GSL effects were larger in the GBA-PD patients carrying GD mutations versus mild mutations. Further studies including clinical outcome studies in GBA-PD patients are planned.

LBA 9
Study Design, Baseline Demographics, and Interim Results from the Prospective Study for Symptomatic Relief of Essential Tremor with Cala Therapy (PROSPECT) Trial
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Objective: To evaluate the durability of symptomatic relief of hand tremor in the treated hand following stimulation with the Cala wearable neuromodulation therapy in essential tremor (ET) patients over a three month trial duration.
Background: The precise mechanisms of ET are uncertain, but it is thought to be caused by abnormal activity within a central tremor network. It has previously been shown that non-invasive electrical stimulation of peripheral nerves that project to this circuit, including the median and radial nerves in the wrist, using the Cala device results in decreased hand tremor in study participants following a single acute 40 minute stimulation session.
Method: PROSPECT was a prospective, multi-center, single-arm, study lasting three months. After screening, patients were fitted with the Cala device on their dominant hand. The stimulation frequency was calibrated based on individual subject's tremor frequency, and stimulation amplitude was increased to individual subject's comfort level. Subjects were instructed to apply the device to their dominant wrist at home twice a day. Each stimulation lasted 40 minutes, and was timed to be performed prior to daily tasks impacted BT ET, such as meals. Subjects were also evaluated in clinic at baseline, and at one month and three month post enrollment. Prespecified co-primary endpoints performed at these clinic visits included the Essential Tremor Rating Assessment Scale (TETRAS) for the treated hand and participant-assessed Bain & Findley Activities of Daily Living (ADLs). Additionally, device sensors measured session time-locked tremor severity during a postural hold before and immediately following stimulation for all at home sessions.
Results: A total of 263 participants were enrolled in the study across 26 US sites. Mean age was 69.6 +/- 10.1 years (23-89) (mean +/- SD; range). Age of ET onset was 43.9 +/- 20.4 (2-79). The study population was 52% female. 62% of participants were on ET medications at study enrollment, which were at stable dose prior to enrollment and throughout the trial. 37% of study participants reported alcohol responsiveness at baseline. Baseline TETRAS for hand subset tasks was 12.5 +/- 2.9 (mean +/- SD). The baseline ADL subset was 18.4 +/- 3.8. Trial enrollment has completed and final subject visits are occurring; initial trial results will be presented.
Conclusion: PROSPECT is the first and largest 3 month study to date to reporting outcomes of a wearable neuromodulation therapy in ET patients. Baseline demographics of subjects enrolled reflected ET patients seen clinically at investigative sites. Study design assessed both in-clinic and at-home endpoints over the three month trial period. Prespecified co-primary endpoints will be presented and their clinical relevance discussed.

LBA 10
The FOsmetpantotenate Replacement Therapy (FORT) Pivotal Trial in Patients with Pantothenate Kinase-Associated Neurodegeneration (PKAN)
T. Klopstock, B. Pérez Dueñas, M. Escolar, H.A. Jinnah, A. Videnovic, G. Zorzi, C. Burns, F. Greblikas (Munich, Germany)
Objective: To evaluate the efficacy and safety of 24 weeks of treatment with fosmetpantotenate in patients with PKAN enrolled in the FORT trial.

Background: PKAN is an autosomal recessive, progressive neurodegenerative disorder with motor and cognitive symptoms. Currently, no approved disease-modifying therapies are available. The FORT trial examines the efficacy and safety of fosmetpantotenate treatment vs placebo in patients with PKAN.

Method: FORT is a phase 3, randomized, double-blind (DB), placebo-controlled pivotal trial of the efficacy and safety of fosmetpantotenate in patients with PKAN (NCT03041116). The FORT trial is a 24-week DB study. Eligible patients have confirmed mutations in the PANK2 gene, are ages 6 to 65 years, with a PKAN-Activities of Daily Living (PKAN-ADL) total score of ≥6. The PKAN-ADL is a novel, validated, 12-item PKAN-specific measure of daily function that was adapted from the Unified Parkinson's Disease Rating Scale (UPDRS) Part II. PKAN-ADL item scores range from 0 (no problem) to 4 (inability to perform activity) and the total score ranges from 0 to 48. The FORT primary efficacy endpoint is change in PKAN-ADL total score from baseline (BL) to end of DB. The secondary efficacy endpoint is change in UPDRS Part III score from BL to end of DB. The Data Monitoring Committee (DMC) conducts pre-planned and periodic safety reviews.

Results: Across 20 study sites in North America and Europe, 84 patients with PKAN (54=adult; 30=pediatric) were randomized to fosmetpantotenate vs placebo. Mean±SD age is 22.9±12.1 (range=6-58) years (adults=29.6±9.7; pediatric=10.7±3.4), 54% of patients are male (adults=52%; pediatric=57%), and 51% are white (adults=56%; pediatric=43%). PKAN-ADL total score (mean±SD) at BL was 27.8±11.4; range=7-48 (adults=25.4±10.5; pediatric=32.2±11.7). Four DMC reviews have been completed, each endorsed continued enrollment of adult and pediatric patients after review of safety data. Topline results will be presented and their impact on the treatment paradigm for PKAN will be discussed.

Conclusion: The FORT trial is a DB placebo-controlled phase 3 study in patients with PKAN. The FORT trial has completed enrollment and randomized 84 patients, making it one of the largest trials to date for this rare, neurodegenerative genetic disorder.

LBA 11

Safety results of an open-label, long-term treatment study of gosuranemab (formerly BIIB092) in participants with PSP

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Objective: To assess safety of gosuranemab in participants with PSP after 24 months of treatment in an open-label (OL), long term extension of a randomized, placebo-controlled study.

Background: Gosuranemab is a humanized IgG4P monoclonal antibody against N-terminal tau, which is found extracellularly in interstitial and cerebrospinal fluid (CSF) and hypothesized to contribute to the spread of tau pathology in PSP. In a randomized, placebo-controlled, phase 1 study (NCT03068468) in participants with PSP, gosuranemab doses up to 2100mg were well tolerated and reduced CSF unbound N-terminal tau by >90% [Boxer Lancet Neurol 2019].

Method: In the placebo-controlled study, 48 participants with PSP received gosuranemab (150, 700 or 2100mg) or placebo intravenously every 4 weeks for 12 weeks. Each dose panel enrolled 8 participants; an additional 24 participants in an expansion panel received 2100mg or placebo. After 12 weeks, 47 participants enrolled in the OL study (NCT02658916), receiving gosuranemab at their original panel dose. Safety parameters (including adverse events [AEs], serious AEs [SAEs], AEs leading to discontinuation, deaths, laboratory tests, vital signs and ECG data) were analyzed by original dose panel from first gosuranemab dose (either in placebo-controlled or OL study).

Results: In total, 63.8% (30/47) of participants had ≥96 weeks of gosuranemab exposure; median (range) exposure was 750 (56-973) days. AEs occurred in 46/47 participants. The most common AEs were fall (reported in 34/47 participants), urinary tract infection (23/47 participants) and contusion (19/47 participants). SAEs (22 events in 16 participants) were reported in 2/8 participants in the 150mg, 3/8 participants in the 700mg and 11/31 participants in the 2100mg groups; all were deemed non-treatment-related by investigators. Four participants had AEs that led to discontinuation: metabolic encephalopathy and aspiration pneumonia (n=1, 150mg), fall (n=1, 2100mg), respiratory arrest (n=1, 2100mg) and aspiration pneumonia (n=1, 2100mg). Four deaths were reported: respiratory arrest (2100mg), aspiration pneumonia (2100mg), cardiorespiratory arrest (2100mg) and PSP (700mg). No apparent dose-related trends in safety parameters or clinically significant abnormalities in vital signs, laboratory tests or ECG were seen.

Conclusion: After a median of 750 days of treatment at doses up to 2100mg, gosuranemab appeared to be well tolerated with an acceptable safety profile. These findings were consistent with safety results in the placebo-controlled study. These data support the continued evaluation of gosuranemab in PSP.

LBA 12
Safety and efficacy of treatment with the anti-aggregative epigallocatechin gallate in patients with multiple system atrophy tested in a multicentric interventional double blinded placebo-controlled trial
J, Levin, A. Giese, W. Oertel, W. Poewe, C. Trenkwalder, G. Wenning, U. Mansmann, PROMESA Study Group, H. Huppertz, I. Ricard, G. Höglinger (Munich, Germany)
Objective: To test safety and efficacy to slow down disease progression of treatment with the anti-aggregative epigallocatechin gallate (EGCG) in patients with multiple system atrophy (MSA).
Background: Intracellular α-synuclein aggregates are the pathological hallmark of a group of neurodegernative synucleinopathies such as MSA. Inhibition of α-synuclein aggregation appears to be a rational approach for developing a disease modifying treatment for synucleinopathies. EGCG is an orally bioavailable polyphenole that inhibits α-synuclein aggregation and shows efficacy in several animal models of synucleinopathies.
Method: A multicentric double-blind placebo-controlled parallel-group study including 92 participants meeting clinical criteria for MSA was conducted. Treatment with EGCG or placebo (randomized block-wise for disease subtypes 1:1) was administered orally for 48 weeks followed. The primary endpoint was the change in motor symptoms assessed by the Unified MSA Rating Scale (UMSARS-ME) from baseline up to 52 weeks.
Results: 127 participants were screened, 92 were randomized and 67 (72.8%) completed treatment. Significantly more liver toxicity was observed in the EGCG group. There was no statistically significant difference in disease progression measured by UMSARS-ME between EGCG and placebo groups at the end of the study. Despite the negative clinical endpoint, we observed a significantly reduced loss in striatal volume in volumetric MRI in EGCG-treated MSA patients compared to controls.
Conclusion: Treatment with EGCG in high doses over 48 weeks did not slow the progression of MSA but led to cases with hepatotoxicity. Biomarker response to treatment in form of reduced atrophy in MRI indicates that treatment approaches with more effective anti-aggregative compounds may be considered for future disease modifying studies in synucleinopathies.
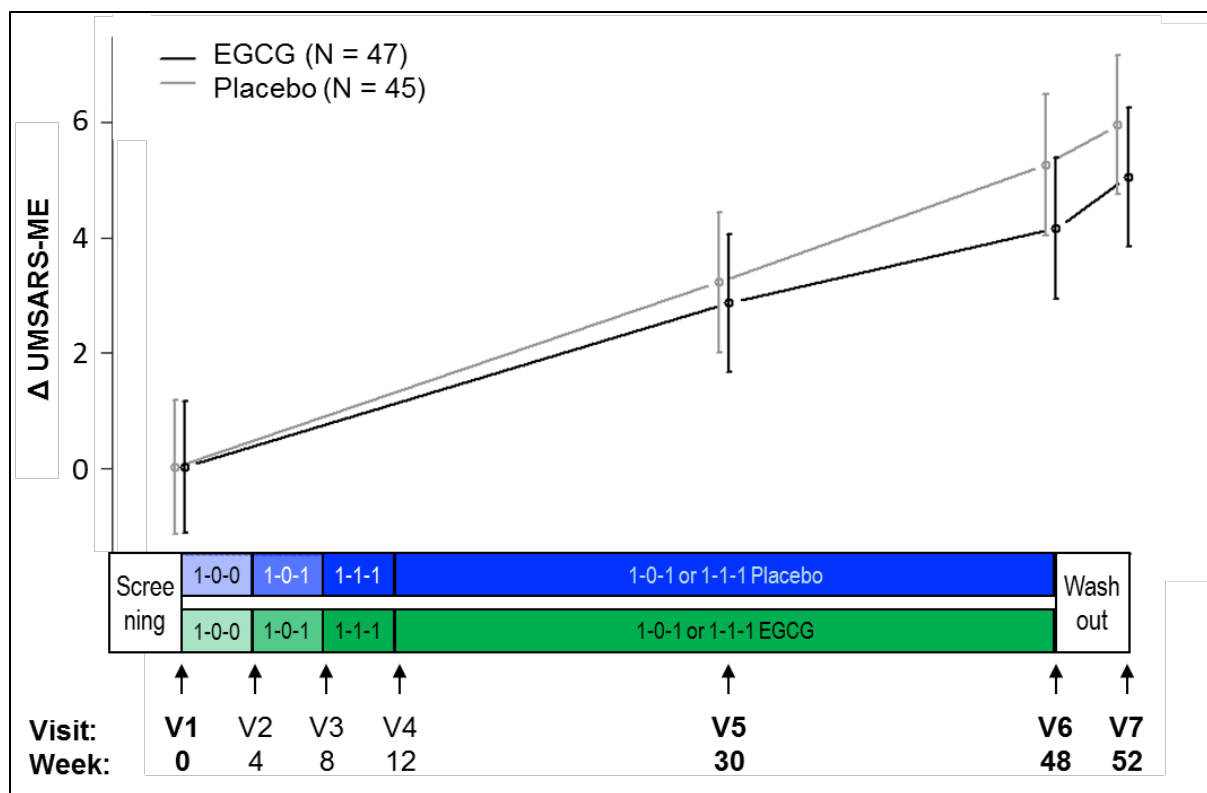
Figure 1

Intention to treat analysis of the PROMESA trial: Change from baseline in UMSARS-ME in the full analysis set. The fitted values are derived from a linear mixed-effect model with MSA phenotype (ie parkinsonism predominant or cerebellar ataxia predominant), treatment, visit (considered here as a factor), and the interaction between visit and treatment as fixed effects, and patients as random effects. Error bars show standard deviation. There is no significant difference in UMSARS-ME progression between the groups. The placebo group shows a linear progression within the expected range suggesting that this trial design would have suited to detect a treatment effect if one had been present. UMSARS=Unified Multiple System Atrophy Rating Scale.

LBA 13
Parkinson's disease causative VPS35 mutation impairs autophagy in vivo
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Objective: Due to an insufficient understanding of the pathogenic mechanisms, there is no treatment that can stop or slow down the progressive neuronal loss in Parkinson's disease (PD) disease. The ultimate goal of this work is to identify new targets in a disease-modifying treatment of PD.
Background: Vacuolar protein sorting 35 (VPS35) is an autosomal dominant causative gene of PD. The protein is a key component of the retromer complex required for endosomal sorting and trafficking of specific cargo proteins. The pathogenic D620N mutation impairs interaction of VPS35 with the Wiskott-Aldrich Syndrome Protein and SCAR Homologue (WASH) complex, composed of WASH1, FAM21, strumpellin, SWIP and CCDC53, but if and how this impaired interaction causes neuronal death is completely unknown.
Method: We used a new transgenic Drosophila model of PD caused by mutant VPS35. Specifically, we tested for locomotor deficits and analyzed the eye phenotype which reliably corresponds to neuronal death.
Results: Here, we show that expressing the D650N mutant form of the Drosophila homologue Vps35 (corresponding to the D620N mutation identified in patients with PD) causes severe locomotor deficits and shortens survival. We next tested our hypothesis that Vps35 is involved in autophagy. In Drosophila

eye, knocking down expression of Vps35, or reducing expression of WASH1, suppressed autophagy activated by overexpressing Atg1. Overexpression of WASH1 or Vps35(WT), but not Vps35(D650N), stimulates autophagy, and this effect is dependent on Atg9. Interestingly, reducing expression of WASH1 and concomitantly overexpressing Vps35(D650N) caused a dramatic increase in autophagy – an effect that was absent with Vps35(WT).

Conclusion: These data suggest that Vps35(WT) stimulates autophagy and that the pathogenic mutant form of VPS35 causes PD by a dominant negative mechanism.

LBA 14
Ambroxol in the modification of Parkinson disease (AiM PD): Results of a phase II non placebo‑controlled trial in genetically stratified Parkinson disease
W. Mullin, L. Smith, K. Lee, G. D'Souza, P. Woodgate, J. Efflein, J. Hallqvist, M. Toffoli, A. Streeter, J. Hosking, W. Heywood, R. Khengar, P. Campell, J. Hehir, S. Cable, K. Mills, H. Zetterberg, P. Limousin, V. Libri, T. Foltynie, T. Schapira (London, United Kingdom)
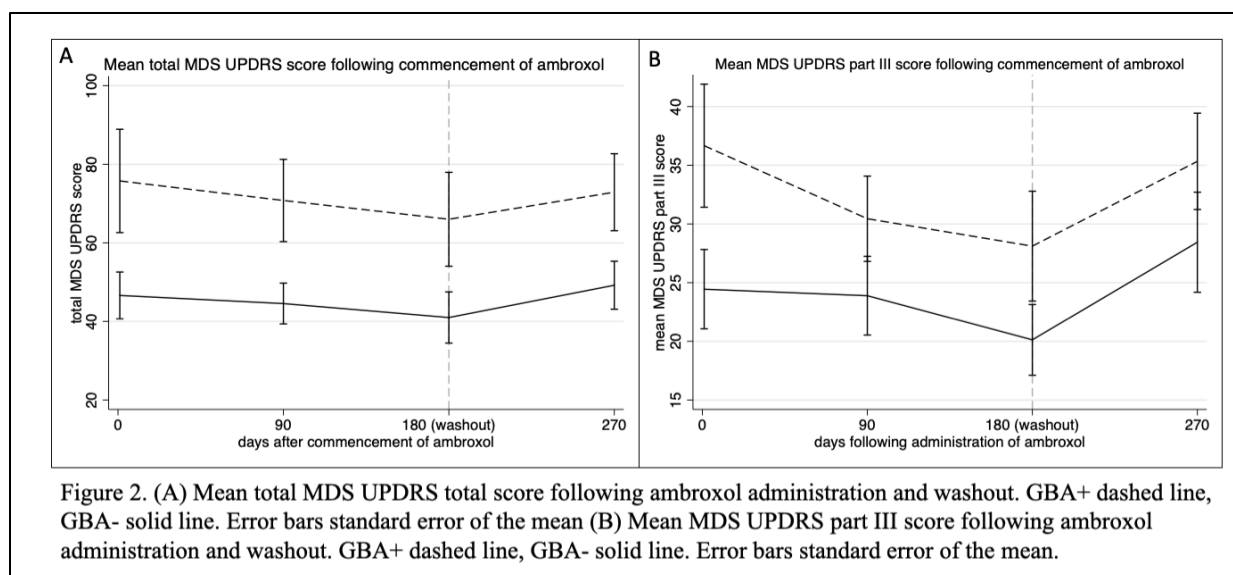**Objective:** To investigate the safety, tolerability, central nervous system (CNS) penetrance and target engagement of ambroxol, a putative neuroprotective compound in Parkinson disease, targeting the glucocerebrosidase (GBA1) pathway.
Background: Mutations in the GBA1 gene, which encodes the glucocerebrosidase enzyme (GCase), are a significant risk factor for Parkinson disease (PD). Evidence suggests that modulation of GCase activity by ambroxol may be neuroprotective.
Method: In this single‑centre, non‑placebo‑controlled trial, patients with moderate PD were administered a 30 day escalating dose of oral ambroxol to 1.26g/day (420 mg TID). Eligible patients had PD, were at Hoehn and Yahr stage 3 or less (on treatment) and were over 18 years. Primary outcomes were to determine safety, tolerability, central nervous system (CNS) penetration and a change in cerebrospinal fluid (CSF) GCase activity. The study is completed (ClinicalTrials.gov: NCT02941822).
Results: Between 11th January 2017, and 25th April 2018, 24 patients were enrolled. Primary analysis included 18 patients (8 GBA1+, 10 GBA1-). Primary outcomes: Ambroxol was well tolerated with no serious adverse events. Between day 0 and 180 mean CSF ambroxol concentration increased by 163ng/mL (SE 13.9, lower 95% CI 192 ng/mL, one‑sided paired t‑test p.
Conclusion: We demonstrate safety, tolerability, CNS penetrance and target engagement of ambroxol. Larger placebo‑controlled trials are required to determine if ambroxol exerts a neuroprotective effect.

A CSF GCase activity pre and post ambroxol exposure

B GCase protein levels pre and post ambroxol exposure

C Mean change in blood leucocyte GCase activity after ambroxol

Figure 1. (A) Box plot (median and IQR) with superimposed data points at baseline and 180 days of GCase activity. GBA1+ black circles. GBA1- white circles. (B) Box plot (median and IQR) with superimposed data points at baseline and 180 days of Gcase protein levels. GBA1+ black circles. GBA1- white circles. (C) Mean change in blood leucocyte GCase activity following administration of ambroxol with error bars (standard error of the mean). GBA+ dashed line, GBA- solid line.

A Mean total MDS UPDRS score following commencement of ambroxol

B Mean MDS UPDRS part III score following commencement of ambroxol

Figure 2. (A) Mean total MDS UPDRS total score following ambroxol administration and washout. GBA+ dashed line, GBA- solid line. Error bars standard error of the mean (B) Mean MDS UPDRS part III score following ambroxol administration and washout. GBA+ dashed line, GBA- solid line. Error bars standard error of the mean.

LBA 15
Nilotinib safety and clinical effects on "ON" disability in Parkinson's disease patients

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Objective: This study evaluated Nilotinib effects on top of the clinical standard of care at 6 and 12 months.

Background: Parkinson's disease (PD) involves motor and non-motor symptoms and loss of brain dopamine neurons. Nilotinib is a brain-penetrant tyrosine kinase inhibitor that may alter brain dopamine metabolism.

Method: A phase II randomized, double-blind, placebo-controlled evaluation of the impact of Nilotinib on safety, tolerability and clinical effects in PD. Seventy-five mid-stage PD participants (H&Y 2.5-3) were randomized 1:1:1 into placebo, 150mg or 300mg Nilotinib once daily for 12 months.

Results: Participants well tolerated Nilotinib and no hematological, hepatic and other systems disorders were observed. Cardiovascular events were seen in all groups. Prior to randomization all participants were stabilized on either Levodopa and/or dopamine agonists and were tested ON time. As expected, all 3 groups were stable at 6 months, indicating the effects of PD medications. However, the placebo group significantly declined on UPDRS II (2.39 points, p=0.007), total UPDRS I-III (4.78 points, p=0.031) and UPDRS I-IV (4.47 points, p=0.038) at 6-12 months but Nilotinib groups remained stable. Similarly, all groups were stable on PDQ39 SI and the emotional well-being subscale at 6 months but the placebo group significantly declined (8.17 points, p=0.001 and 1.7 points, p=0.03, respectively) at 6-12 months, while Nilotinib groups remained stable.

Conclusion: Nilotinib is well tolerated and appears to be safe in PD patients. Nilotinib appears to stop the decline in motor and non-motor functions when the effects of PD medications wear off six months after treatment. Nilotinib may have a significant impact on the care and management of PD patients, leading to delay or elimination of dose adjustment, thus avoiding various side effects associated with PD-medications.

LBA 16
Safety, Pharmacokinetics, and Pharmacodynamics of Oral Venglustat in the Japanese and the Rest of the World Parkinson's Disease Population with a *GBA* Mutation: Results from Part 1 of the MOVES-PD Study

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Objective: To assess the safety, pharmacokinetics (PK), and pharmacodynamics of oral venglustat in Parkinson's disease (PD) patients with a glucocerebrosidase (*GBA*) mutation from Japan and the rest of the world (ROW).

Background: A heterozygous mutation in *GBA* predisposes PD patients to cognitive impairment and rapid disease progression at a younger age [1]. Venglustat is a glucosylceramide (GL-1) synthase inhibitor investigated in PD patients with a *GBA* mutation.

Methods: Part 1 of the phase 2 MOVES-PD trial (NCT02906020) was a randomized, placebo-controlled, double-blind, sequential cohort study of venglustat at 3 escalating doses in PD patients ≥18 years with a *GBA* mutation. Venglustat doses were evaluated separately in Japanese patients (per regulatory agency request) to ensure consistency with ROW population. Venglustat/placebo was administered for up to 36 weeks in ROW population and 52 weeks in Japanese patients. Assessments: venglustat safety/tolerability (primary endpoint); plasma and cerebrospinal fluid (CSF) PK and pharmacodynamics.

Results: A total of 29 PD patients were randomized to venglustat (Japan [n=9]; ROW [n=13]) or placebo (Japan [n=3]; ROW [n=4]). Mean age was 54.3 years (Japan) and 58.4 years (ROW); mean time since PD symptom onset was 6.7 years, and since diagnosis was 5.2 years in both populations. Eight (89%) Japanese venglustat-treated patients, and 12 (92%) ROW patients reported ≥1 treatment-emergent AE (TEAE) versus 2 (67%) and 4 (100%) patients from the respective placebo groups; most TEAEs were mild/moderate and resolved without corrective treatment. Psychiatric, gastrointestinal, and neurological events, consistent with common motor/non-motor PD symptoms or known AEs of concurrent PD

medications, were the most common TEAEs in both populations. No serious AEs or deaths occurred. No Japanese patients and 2 ROW patients on venglustat discontinued due to TEAEs after Week 4 (primary timepoint). In both populations, venglustat exposure in plasma and CSF increased in a close to dose-proportional manner, and plasma and CSF GL-1 levels decreased from baseline in a dose-dependent manner over 4 weeks. At the highest dose, CSF GL-1 decreased 72.0% in Japanese and 74.3% in ROW patients.

Conclusions: All doses of venglustat demonstrated favorable safety and tolerability in Japanese and ROW PD patients, with dose-dependent plasma and CSF exposure, and reduction in plasma and CSF GL-1. Part 2 of MOVES-PD is ongoing.

References: 1. Cilia R, Tunesi S, Marotta G, et al. Survival and Dementia in GBA-associated Parkinson's Disease: The Mutation Matters. Ann Neurol. 2016; 80: 662–673.

LBA 17
Novel PET data and analysis of early HD from PRIDE-HD
R. Reilmann, W. Olanow, A. McGarry, M. Geva, M. Leinonen, M. Hayden, O. Sabri, P. Meyer, I. Grachev, K. Kieburtz, L. Raymond, F. Saudou (Herzliya, Israel)

Objective: To analyze the effect of pridopidine (45 mg bid) on Total Functional Capacity (a measure of HD stage) in patients with early HD (HD1+HD2, TFC 7-13) and to determine the in-vivo target engagement at this dose.

Background: Pridopidine is a selective Sigma-1 Receptor (S1R) agonist regulating pathways impaired in neurodegeneration including BDNF secretion. BDNF is reduced in brains of HD patients and animal models. BDNF overexpression alleviates disease features in HD mice.

Method: Pridopidine effects on BDNF, synaptic plasticity and neuronal survival were evaluated in preclinical models of neurodegeneration including the 6-OHDA (PD) and YAC128 (HD) mice, and in cellular models of HD. The role of S1R was assessed by looking at the effects of S1RKO mice and pharmacological inhibition on endpoints. In-vivo S1R target engagement was determined in humans by PET imaging using the S1R-specific (S)-(-)-[18F] Fluspidine ligand and compared to D2/3R-specific [18F] Fallypride. Post-hoc exploratory analysis of the 45 mg bid dose from PRIDE-HD in early HD patients determined the effect of pridopidine on TFC and Q-motor (placebo independent assessment of motor function).

Results: Pridopidine increases BDNF protein (in PD mice and neuroblastoma cells), axonal transport (HD neurons) and the BDNF downstream signaling pathways including p-ERK and CREB pathway. Furthermore, pridopidine rescues synaptic plasticity in HD cortical neurons.
At 45 mg bid pridopidine selectively binds the S1R as seen by PET imaging (>90% S1R vs 3% D2/3R binding). Exploratory post-hoc analysis from PRIDE-HD, shows that the 45 mg bid dose significantly reduces TFC decline in early HD patients (HD1+2) at 52wks (Δ1.16 to placebo p=0.0003). While TMS show a positive trend, it is masked by a high placebo effect. However, multiple Q-motor measures supports motor effect of pridopidine in early HD.

Conclusion: Pridopidine acts as a S1R agonist, enhancing neuroprotective effects in animal models of PD, HD and AD. At the clinical dose of 45 mg bid pridopidine shows full and selective S1R occupancy. This dose significantly reduces rate of TFC decline compared to placebo in early HD patients. These data support further investigation of pridopidine on TFC in HD.

LBA 18
Directional versus conventional Deep Brain Stimulation: Results of a multi‑center prospective blinded crossover study
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Objective: To determine if there is a difference in the range of stimulation amplitudes that can relieve symptoms without side effects for directional Deep Brain Stimulation (DBS), compared to conventional omnidirectional stimulation.

Background: Recently introduced directional DBS leads have the two middle contacts divided into three segments. These systems may deliver conventional stimulation using all three segments of the contact,

or directional stimulation using one or two segments. Published reports on directional DBS have been limited to small series from single-center investigations. To confirm clinical usefulness of directional stimulation, therapeutic window (TW) can be used as a surrogate outcome measure. Wider TW suggests greater programming flexibility to achieve symptom relief with limited side effects. PROGRESS specifically addresses this question by evaluating safety and clinical efficacy of directional DBS in a large prospective cohort.

Method: Directional and conventional stimulation were prospectively compared in patients receiving subthalamic nucleus DBS for Parkinson's disease. Participants were programmed with conventional stimulation for 3 months, followed by directional for 3 months. Both the subject and evaluator were blinded to stimulation type. The primary endpoint compared TW, defined as the difference in amplitude between sustained side effect threshold and minimum therapeutic current, for directional vs. conventional stimulation. Additional endpoints at 3- and 6-month follow-ups included subject and clinician stimulation preference, therapeutic current strength, UPDRS part III motor score, activities of daily living and quality of life.

Results: In preliminary results on the full cohort (N=208), therapeutic window was wider with directional stimulation (2.80±1.44mA) compared to conventional stimulation (2.12±1.34mA, p<0.001). Amongst participants who have completed the 6-month visit (N=162), 85 preferred the period with directional stimulation (52%) and 41 favored the period of conventional stimulation (25%). Clinicians favored the directional period for 95 participants (59%), and conventional for only 33 cases (20%).

Conclusion: In this international prospective blinded crossover study, it was shown that directional stimulation yielded wider TW than conventional stimulation, which may have implications for DBS programming using directional leads. This abstract will be supplemented with complete results for the full study cohort through 6 months of follow-up.

LBA 19

Safety and Tolerability During a 4-Week Continuous Subcutaneous Infusion of ABBV-951, a New Drug Formulation for the Treatment of Parkinson's Disease: Final Results of a Phase 1b Study
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Objective: Evaluate the safety and tolerability of ABBV-951 delivered via continuous subcutaneous infusion (CSCI) in Parkinson's disease (PD) patients.

Background: ABBV-951 is a new solution of carbidopa and levodopa prodrugs for continuous subcutaneous delivery. In previous Phase 1 studies, ABBV-951 was generally well tolerated in healthy volunteers and PD patients. Here we assess the safety profile of individually titrated therapeutic doses of ABBV-951 administered to PD patients via 24-hour CSCI for 28 days in an outpatient setting.

Method: Eligible subjects for this Phase 1b, open-label, single-arm study (NCT03374917) were PD patients whose motor complications were inadequately controlled by oral medications and who experienced a minimum of 2.5 h/day of "Off" time. A screening and titration period were followed by weekly study visits. Local and systemic safety and tolerability were assessed by the infusion site assessment 2-part rating scale (numeric scores: 0-7 and letter grades: A-G) and adverse event (AE) monitoring. Exploratory efficacy was also assessed by the mean change from baseline in MDS-UPDRS scores and patient PD Diaries.

Results: As of April 2019, a total of 21 patients from 9 study sites in the United States (62% male, mean age 61.6, 43% with ≥10 years PD duration) were included in the safety analysis. AEs (mild to moderate in severity) occurred in 19 patients (90.5%); 2 serious AEs (cellulitis and abdominal abscess) were reported in 1 patient, who prematurely discontinued the study. Another patient prematurely discontinued due to an AE of infusion site infection. Five patients (24%) had Numeric Score ≥3 or Letter Grade ≥C on the Infusion Site Evaluation Scale; all other patients were classified as 0, 1, or 2 score or A or B grade, consistent with findings reported for other CSCI therapies. There were no clinically significant changes in laboratory, ECG, or vital sign parameters. ABBV-951 doses ranged from 400 mg to 3400 mg levodopa equivalents and support the preliminary results of efficacy which showed improvement comparable to that obtained with other PD therapies.

Conclusion: These results demonstrate that ABBV-951 is safe and tolerable when delivered via 24-hour CSCI for 28 days and support future investigations of ABBV-951 as a potentially new treatment option for PD patients.

LBA 20

Improvements in Dyskinesia with Levodopa-Carbidopa Intestinal Gel in Advanced Parkinson's Disease Patients in a 'Real-World' Study: Interim Results of the Multinational DUOGLOBE Study With up to 24 Months Follow-Up

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Objective: Evaluate the effect of levodopa-carbidopa intestinal gel (LCIG) on dyskinesia symptoms as well as quality of life (QoL) and caregiver burden in a multicountry observational study in advanced Parkinson's disease (aPD) patients treated with LCIG in routine clinical practice.

Background: As PD progresses, chronic oral levodopa therapy can be associated with disabling motor complications including wearing off and dyskinesia. LCIG has established benefit in reducing "Off" time, but prospective long-term data on the effect of LCIG on dyskinesia symptoms and associated effects on QoL and caregiver burden in a real-world setting are limited.

Method: DUOGLOBE is a prospective multinational observational study (including US sites) of LCIG naïve patients treated as part of routine clinical practice with 3-years follow-up planned (NCT02611713). This is the first multinational LCIG study using the Unified Dyskinesia Rating Scale (UDysRS), a novel validated scale for dyskinesia. Other assessments included the UPDRS Part IV, "Off" time, Non-Motor Symptoms Scale (NMSS), QoL (8-item PD questionnaire [PDQ-8]), Modified Caregiver Strain Index, and Serious Adverse Events (SAEs). Interim outcomes from baseline up to month (M) 24 are presented.

Results: In this interim analysis, 196 patients were included (62% male, 78% ≥65 years old; 51% ≥10 years' PD duration. Median daily duration of LCIG infusion was 16.0 h/d LCIG through M24, with up to 9% of patients on 24h LCIG infusion. Significant improvements (mean change from baseline to M24) were observed in "Off" time (-3.6 h/d) and NMSS total scores (-27.0). LCIG treatment significantly improved dyskinesia symptoms and signs assessed by the UDysRS and UPDRS Part IV items 33 and 34 through M18 [Figure 1]. QoL and caregiver burden [Figure 2] were also improved through M18. Overall, 41% of patients experienced SAEs [Table 1]; 31% (n=60) discontinued participation in DUOGLOBE with 13 patients continuing LCIG outside the study.

Conclusion: This interim analysis shows sustained improvements of dyskinesia symptoms and signs, measured using the UDysRS, with LCIG in routine clinical practice and supports the real-world effectiveness of LCIG on "Off" time, NMS, QoL, and caregiver burden in aPD patients. Safety was consistent with the established LCIG profile.
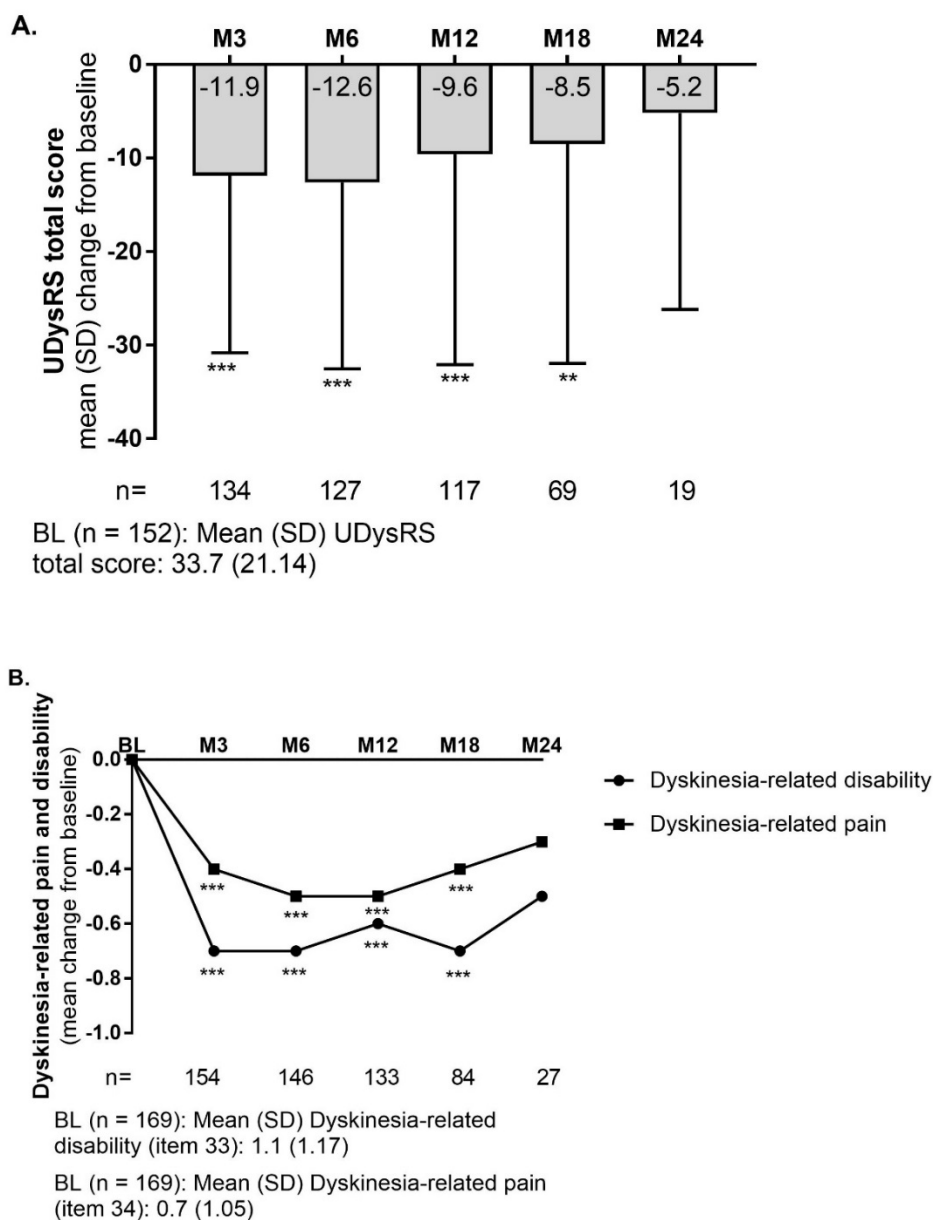
Figure 1. Mean (SD) change from baseline at regularly schedule visits for dyskinesia symptoms assessed by (A) UDysRS and (B) UPDRS Part IV. BL = baseline; M = month; SD = standard deviation; UDysRS = Unified Dyskinesia Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale. ***, ** statistically significant at P < .001, P < .01, respectively.
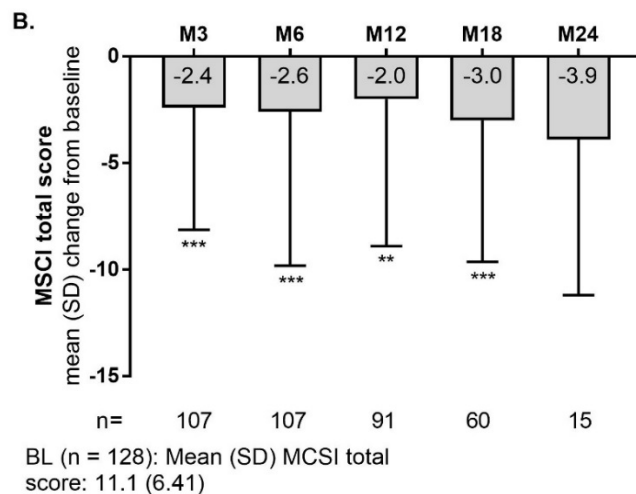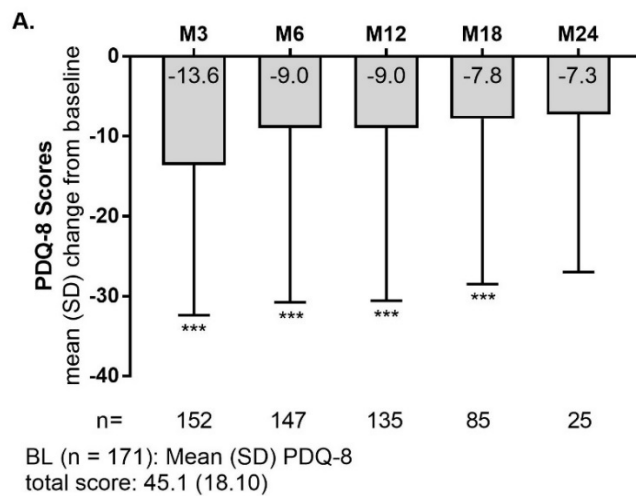
Figure 2. Mean (SD) change from baseline at regularly schedule visits for QoL and caregiver burden as assessed by (A) PDQ-8 and (B) MCSI scores. BL = baseline; MCSI = Modified Caregiver Burden Index; M = month; 8-part Parkinson's Disease Questionnaire; SD = standard deviation. ***, ** statistically significant at P < .001 and P < .01, respectively.

Table 1. Treatment-Emergent Serious Adverse Events

	Patients, n (%) N=196
Subjects with:	
Any severe AE	46 (23.5)
Any SAE	80 (40.8)
Any SAE with reasonable possibility of causal relationship with LCIG	24 (12.2)
Any AE leading to drug being withdrawn	29 (14.8)
Deaths	13 (6.6)
Deaths considered to be related to the treatment by the study investigator[a]	1 (0.5)

	SAEs n (%)	Treatment-related SAEs (Reasonable Possibility) n (%)
Patients with any SAE	80 (40.8)	24 (12.2)
SAEs occurring in >1% of patients in MedDRA system organ classes of interest		
Gastrointestinal disorders	18 (9.2)	10 (5.1)
Abdominal pain	4 (2.0)	3 (1.5)
Pneumoperitoneum	3 (1.5)	2 (1.0)
Product issues	9 (4.6)	7 (3.6)
Device dislocations	3 (1.5)	2 (1.0)
Device occlusion	3 (1.5)	2 (1.0)
Nervous system disorders	16 (8.2)	2 (1.0)
Neuropathy[b, c]	3 (1.5)	0

[a]abdominal obstruction; [b]chronic inflammatory demyelinating polyradiculoneuropathy (n=1), polyneuropathy (n=1), and sensory loss (n=1); [c]all 3 neuropathies were judged by the investigator as not treatment related.

AE = adverse event; LCIG = levodopa-carbidopa intestinal gel; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

LBA 21
Biomarker Development in Pre-Symptomatic Plasma from Parkinsonian Patients
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Objective: Our overall goal is to identify and validate pre-symptomatic PD biomarkers in plasma. This will be done in steps and in collaboration to identify protein biomarkers in CSF and blood from patients with parkinsonian disorders and then validate these in the pre-symptomatic samples.
Background: Northern Sweden Health and Disease Study (NSHDS) is a biobank started in 1988 that includes plasma samples from about 130 000 healthy volunteers. The clinical registry of NSHDS has been thoroughly reviewed to identify 500 parkinsonian patients that submitted pre-symptomatic samples.
Method: Mass spectrometry (MS) proteomic methods have been used for untargeted profiling of parkinsonian patients with both CSF and plasma depleted of high-abundant proteins (HAP). CSF and blood samples from patients with PD, multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and healthy volunteers were depleted of HAPs with TOP2 spin columns (Pierce) or a multiple affinity removal system (MARS) HPLC column (Agilent). Candidate biomarkers identified in discovery experiments, literature surveys and biological pathway analysis were selected for validation experiments. MS-based multiple reaction monitoring (MRM) assays were developed for more than 100 peptides using stable-isotope labeled standard (SIS) peptides. These MRM assays were evaluated for technical robustness, sensitivity to sample processing and normal physiological variation.

Results: MRM validation experiments in CSF and blood were performed to identify the most significantly altered biomarkers in PD, PSP and MSA. Multiplexed assays were developed to robustly quantify 47 peptides in CSF, and more than 30 in blood, including proteins involved in mitochondrial and metabolic function, protein homeostasis, cytoskeletal integrity and immune activation. Multivariate modeling using SIMCA software identified optimized sets of biomarker candidates for each disease to be tested in pre-symptomatic samples. Identified NSHDS plasma samples were combined with post-diagnosis biobank samples from the same patients into 2 atypical cohorts (MSA/PSP/control and DLB/control) and 2 PD cohorts (test and validation; about 800 samples each).

Conclusion: We have identified protein biomarker candidates in post-symptomatic samples from patients with parkinsonian disorders which warrant detailed analysis in pre-symptomatic samples. But biomarker differences were more pronounced in more rapidly progressing diseases (MSA and PSP) or at later stages of PD, suggesting that fewer will be validated in the earlier stages of disease. This indicates that novel discovery experiments need to be performed using the pre-symptomatic samples. These can include antibody or affinity-based profiling arrays and additional MS-based untargeted profiling methods. Validation assays should include MRM, immunoMRM and antibody-based assays. Pre-symptomatic protein biomarkers can reveal the earliest molecular changes in disease and identify novel drug targets.

LBA 22
Identification of clinically imperceptible Parkinson's bradykinesia using wearable sensors and machine learning: clinical implications
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Objective: To investigate the effectiveness of a machine learning derived classifier in discriminating undetectable bradykinesia in the unaffected side of Parkinson's disease (PD) patients from normal controls (NC), determine drug efficiency in early-stage PD and identify the movement characteristics of PD that contrast with multiple systematic atrophy (MSA), in the hospital environment where conventional visual inspection alone is unable to make a reliable classification.

Background: Previous studies suggest that wearable sensors can provide a quantitative and reliable method for evaluating a PD patient's motor performance [1]. Our previous research, conducted using a simple-to-use device employing a classifier derived from a machine learning evolutionary algorithm (EA) [2], has motivated us to determine its ability to distinguish slight nuances in PD patients and to identify those movement characteristics that might discriminate between PD with other atypical parkinsonism, including MSA.

Method: 269 right-handed PD, 52 right-handed MSA and 153 right-handed age-matched NC were enrolled in our study, of which 32 PD (early stage and within small-dose medication) volunteered to be tested after a minimum of 12 hours drug withdrawal and retested one hour after taking medication [Table 1]. A standard finger tapping (FT) task was measured for 30 seconds in each hand using electromagnetic tracking sensors ("PD-Monitor" [3]), attached to the subject's thumb and index finger. FT was rated clinically by two qualified neurologists according to the Movement Disorder Society sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) FT item.

Results: In regard to the visually undetectable bradykinesia in FT (unilateral FT score= 0), the PD-Monitor score showed significant differences compared to the ipsilateral side in NC (left side: P $<$ 0.001; right side: P $<$ 0.001；two-tailed unpaired t test) [Figure 1]. Moreover, in order to evaluate PD-Monitor's efficacy in detecting rarely-detected subjective improvements in FT scores, only those patients whose subjective FT score improvement cannot be identified by neurologists among the 32 PD were included (28 in the left side, 30 in the right side), and yet significant improvements were still noted in the PD-Monitor recorded score (left side: P = 0.011; right side: P $<$ 0.001; two-tailed paired t test) [Figure 2]. However, the inter-group difference in movement characteristics between PD and MSA cannot be discriminated by the current EA-based classifier. This is despite the ability of the EA-based classifier being able to detect a difference in severity of bradykinesia between MSA and NC (AUC≥74.1% according to the receiver operating characteristic curve) [Figure 3].

Conclusion: This study further elucidates the practical potential of PD-Monitor to differentiate bradykinesia so minimal that it cannot be recognized through visual inspection alone. It also identifies and

confirms the efficacy of PD-Monitor in identifying subjective undetectable improvement in FT bradykinesia over a short time period, thus highlighting its potential to discriminate the disease-modifying effect of treatment. However, PD-Monitor's current classifier is not effective in differentiating between PD and MSA, which has been specifically developed and trained to discriminate between PD and NC. Current work is investigating newly trained EA classifiers to further identify those Parkinson's specific movement patterns that can discriminate between PD and other atypical parkinsonism, such as MSA and progressive supranuclear palsy (PSP).

References: 1. Kubota, K. J., Chen, J. A., et al. (2016). Machine learning for large-scale wearable sensor data in Parkinson's disease: Concepts, promises, pitfalls, and futures. Mov Disord, 31(9), 1314-1326. doi:10.1002/mds.26693

2. Gao, C., Smith, S., et al. (2018). Objective assessment of bradykinesia in Parkinson's disease using evolutionary algorithms: clinical validation. Transl Neurodegener, 7, 18. doi:10.1186/s40035-018-0124-x

3. ClearSky Medical Diagnostics Ltd., York, UK: www.clearskymd.com

Table 1 Demographic and clinical data of the study participants				
	PD	**MSA**	**NC**	*P* value
Overall subjects				
Numbers	N = 269	N = 52	N = 153	
Gender[female, %]	135(50.2)	20(38.5)	80(52.3)	0.217
Age[years]	62.6±9.6	62.8±8.0	61.8±8.9	0.570
Disease durations[years]	4.7±4.1	4.1±3.1	NA	0.926
LEDD[mg]	323.7±276.4	370.1±306.0	NA	0.298
Subgroup of PD (FT=0) vs. NC				
Left(FT=0) as the tested side				
Numbers	N = 123		N = 153	
Gender[female, %]	62(50.4)		80(52.3)	0.756
Age[years]	62.6±9.7		61.8±8.9	0.134
Right(FT=0) as the tested side				
Numbers	N = 115		N = 153	
Gender[female, %]	65(56.5)		80(52.3)	0.491
Age[years]	62.3±9.4		61.8±8.9	0.129
MSA vs. NC				
Numbers		N = 52	N = 153	
Gender[female, %]		20(38.5)	80(52.3)	0.085
Age[years]		62.8±8.0	61.8±8.9	0.557
PD vs. MSA				
Numbers	N = 269	N = 52		
Gender[female, %]	135(50.2)	20(38.5)		0.121
Age[years]	62.6±9.6	62.8±8.0		0.870
Disease durations[years]	4.7±4.1	4.1±3.1		0.926
LEDD[mg]	323.7±276.4	370.1±306.0		0.298
Early-stage PD tested before and one hour after small-dose medication				
Numbers	N = 32			
Gender[female, %]	22(68.8)			
Age[years]	62.5±8.5			
Disease durations[years]	2.3±1.2			
LEDD[mg]	193.0±147.2			

Kruskal-Wallis test or Mann-Whitney U test was used to compare the continuous variables
Chi-square test was used to compare the categorical variables, as appropriate. Quantitativ

Figure 1 PD-Monitor FT scores in undetectable bradykinesia (FT = 0) according to MDS-UPDRS showed a significant deterioration in comparison between compared to the ipsilateral side in NC. A) Left side, 123 PD with unilateral FT rating 0 vs. NC; B) Right side, 115 PD with unilateral FT rating 0 vs. NC. Values are means $\pm$ SEMs (two-tailed unpaired t test). *** indicates $P <$ 0.001. PD, Parkinson's disease; NC, normal control; FT, finger tapping; MDS-UPDRS, Movement Disorder Society sponsored Unified Parkinson's Disease Rating Scale; SEM, standard error of mean.

Figure 2 PD-Monitor FT scores revealed significant improvements in bradykinesia among 32 PD during low-dosage monotherapy in early stage (H-Y stage⩽2.5) in comparison between drug withdrawal more than 12 hours (off period) and one hour after relatively small-dose medication (on period). A) Left side, after the exclusion of 4 PD whose subjective FT scores were improved, 28 PD before and after medication (off-on period comparison); B) Right side, after the exclusion of 2 PD whose subjective FT scores were improved, 30 PD before and one hour after medication (off-on period comparison); C) Left side, 10 representative PD before and after medication (off-on period comparison); D) Right side, 10 representative PD before and after medication (off-on period comparison). Values are means $\pm$ SEMs (two-tailed paired t test). *** indicates $P < 0.001$, * indicates $P < 0.05$. PD, Parkinson's disease; NC, normal control; FT, finger tapping; H-Y stage, Hoehn and Yahr stage; SEM, standard error of mean.

Figure 3 PD-Monitor FT scores identified different severity of bradykinesia in MSA. The ROC curves visualized strong separation between overall MSA and NC, as well as between each subgroup (FT≤1, FT≤2, FT≤3) of MSA and NC. A) Left side, All MSA vs. NC: AUC=0.827, sensitivity=69.2%, accuracy=79.5%, specificity=85.6%, cutoff=0.090; MSA (FT≤1) vs. NC: AUC=0.742, sensitivity=85.2%, accuracy=63.9%, specificity=60.1%, cutoff=-0.132; MSA (FT≤2) vs. NC: AUC=0.811, sensitivity=90.7%, accuracy=58.7%, specificity=60.1%, cutoff=-0.132; MSA (FT≤3) vs. NC: AUC=0.824, sensitivity=68.6%, accuracy=81.4%, specificity=85.6%, cutoff=0.090; all with $P < 0.001$. B) Right side, All MSA vs. NC: AUC=0.840, sensitivity=73.1%, accuracy=82.4%, specificity=85.6%, cutoff=0.038; MSA (FT≤1) vs. NC: AUC=0.741, sensitivity=73.1%, accuracy=75.4%, specificity=75.8%, cutoff=-0.048 ; MSA (FT≤2) vs. NC: AUC=0.798, sensitivity=77.5%, accuracy=76.2%, specificity=75.8%, cutoff=-0.048; MSA (FT≤3) vs. NC: AUC=0.837, sensitivity=72.6%, accuracy=78.4%, specificity=85.6%, cutoff=0; all with $P < 0.001$. PD, Parkinson's disease; MSA, multiple systematic atrophy; NC, normal control; FT, finger tapping; ROC receiver operating characteristics; AUC, area under the ROC curve.