LATE-BREAKING ABSTRACTS

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MDS Virtual Congress 2021 Late-Breaking Abstracts

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Deterministic tractography-based versus indirect-targeting magnetic resonance-guided focused ultrasound treatment of medication-refractory essential tremor: 3-year results of a prospective cohort study
F. Cheng, C. Xu, B. Jiang, B-L. Zhang, G. Huo, K. Tang (*Kingston upon Hull, United Kingdom*)

LBA 1

Triheptanoin is associated with clinical stability and decreased caudate atrophy in Huntington disease

F. Mochel, A. Meneret, I. Adanyeguh, C. Giron, E. Hainque, MP. Luton, M. Atencio, M. Barbier, M. Jacobs, FCM. Veldkamp, E. Coppen, A. Kampstra, JY. Winder, KF. van der Zwaan, E. Vicaut, R. Roos, A. Durr (*Paris, France*)

Objective: To assess the efficacy of triheptanoin, a medium chain triglyceride with an odd number of carbons that targets the Krebs cycle, on key brain imaging and clinical measures in Huntington disease (HD).
Background: We previously showed that energy deficit in HD is associated with increased substrate requirements for the Krebs cycle (1). Using 31 phosphorus brain MR spectroscopy, we then demonstrated that triheptanoin can restore a normal brain energetic profile in HD patients (2).
Method: To ensure acceptability for patients, we conducted a 6-month randomized controlled bi-centric trial (Paris and Leiden) called TRIHEP3 (NCT02453061), comparing triheptanoin 1g/kg/day vs. placebo in 100 patients (ratio 1/1) at an early stage of HD, followed by a 6-month open label phase. After one year, patients could opt for a one-year extension study. The primary outcome measure was the rate of caudate atrophy at 6 months using cBSI (caudate boundary shift integral). Secondary outcome measures were cBSI at 12 and 24 months, total motor score (TMS) of the UHDRS, and diffusion imaging using both Diffusion Tensor Imaging (DTI) and Fixel-Based Analysis (FBA), which allows the analysis of crossing fibers, at 6, 12 and 24 months. To perform a comparative analysis of triheptanoin versus placebo over one year, we used the placebo arm of a one-year randomized controlled trial (NCT02336633), conducted in parallel with identical methods, in HD patients with similar clinical characteristics (age, disease duration, TMS, CAG repeats).
Results: 86 patients completed the one-year TRIHEP3 study and 42 completed the consecutive 12-month extension. Triheptanoin was well tolerated. Side effects were mainly gastrointestinal issues, which usually resolved with dietary management. We saw no difference in cBSI at 6 months between triheptanoin and placebo. TMS at 12 months tended to stabilize in patients treated with triheptanoin for one year (mean 0.6 ± 5.1) compared to patients treated for only 6 months (2.5 ± 4.5) ($p= 0.072$), with a significant difference between 6 and 12 months (-0.7 ± 3.9 vs 1.9 ± 4.7, $p= 0.024$). DTI and FBA analyses showed fewer alterations in fiber metrics at 24 months in patients treated from baseline, and FBA showed improved fiber trophicity at 24 months in both groups. Compared to the external placebo control group, at one year, TMS confirmed clinical stability in patients treated with triheptanoin (2.6 ± 4.6 vs 0.6 ± 5.1, $p= 0.057$) and caudate atrophy was significantly less (-3% vs -6.7% compared to baseline, $p< 0.001$) (Figure 1).
Conclusion: Taken together, these results showed that treatment with triheptanoin was associated with clinical stability (UHDRS) and decreased caudate atrophy in HD patients.
References: (1) Early energy deficit in Huntington disease: identification of a plasma biomarker traceable during disease progression. Mochel F, Charles P, Seguin F, Barritault J, Coussieu C, Perin L, Le Bouc Y, Gervais C, Carcelain G, Vassault A, Feingold J, Rabier D, Durr A. PLoS One. 2007 Jul 25;2(7):e647. (2) Triheptanoin improves brain energy metabolism in patients with Huntington disease. Adanyeguh IM, Rinaldi D, Henry PG, Caillet S, Valabregue R, Durr A, Mochel F. Neurology. 2015 Feb 3;84(5):490-5.

LBA 2
Efficacy of Omaveloxolone in Patients with Friedreich's Ataxia: Delayed-Start Study

D. Lynch, M. Chin, S. Boesch, M. Delatycki, P. Giunti, A. Goldsberry, C. Hoyle, C. Mariotti,K. Matthews, W. Nachbauer, M. O'Grady,S. Perlman, S. Subramony, T. Zesiewicz, C. Meyer (*Philadelphia, PA, USA*)

Objective: The objective of the delayed-start study was to evaluate the efficacy of omaveloxolone treatment in patients with Friedreich's Ataxia (FRDA) by comparing the difference in mFARS scores at the end of a 48-week placebo-controlled period with the difference after 72 weeks in an open-label delayed-start period for patients initially randomized to omaveloxolone versus those initially randomized to placebo.
Background: MOXIe (408-C-1402; NCT02255435) was a 2-part study designed to evaluate the safety and efficacy of omaveloxolone in patients with FRDA, a rare, serious neurological disease with no available therapies. MOXIe Part 1 was a dose-finding study, and the MOXIe Part 2 study showed omaveloxolone significantly improved modified Friedreich's Ataxia Rating Scale (mFARS) scores by 2.40 points relative to placebo after 48 weeks of treatment (p=0.014; n=82). Patients in both study parts were eligible to receive omaveloxolone in the open-label extension study and investigators and patients remained blinded to prior patient treatment assignments.
Method: We compared the difference in mFARS scores between treatment groups (placebo to omaveloxolone versus omaveloxolone to omaveloxolone) using a single mixed model repeated measures (MMRM) model for all available data from both the 48-week placebo-controlled period (MOXIe Part 2) and the 72-week open-label, delayed-start period (MOXIe Extension).
Results: A total of 73/75 (97%) patients in the Full Analysis Set (i.e., patients without severe pes cavus) who completed MOXIe Part 2 enrolled in the Extension study, including 39 patients previously randomized to placebo and 34 patients previously randomized to omaveloxolone. The difference in mFARS between omaveloxolone and placebo observed at the end of the placebo-controlled MOXIe Part 2 (-2.18 ± 0.96 points) was preserved at the end of the delayed-start period (-2.92 ± 2.13 points). Patients in the placebo to omaveloxolone group had annualized mFARS slopes (0.27 ± 0.63 points) that were similar to the omaveloxolone to omaveloxolone group (0.17 ± 0.61 points); both slopes were less than the expected +1.9 points per year observed in natural history data. Additionally, patients previously randomized to omaveloxolone in MOXIe Part 2 continued to show no worsening in mFARS relative to their original baseline through 120 weeks (nearly two and half years) of treatment.
Conclusion: The results of this study support the positive primary endpoint findings in the pivotal MOXIe Part 2 trial and indicate a persistent effect of omaveloxolone treatment on disease course in FRDA.

LBA 3
Omics profile of iPSC-derived astrocytes from Progressive Supranuclear Palsy (PSP) patients

FG. Ravagnani, HP. Valerio, AN. de Oliveira, RD. Puga, KG. Oliveira, AL. Sertie, LL. de Lira, HB. Ferraz, RR. Catharino, GE. Ronsein, MC. Aguiar (*São Paulo, Brazil*)

Objective: We aimed to develop a model of induced pluripotent stem cells (iPSC)-derived astrocytes to investigate the pathophysiology of PSP, particularly early events that might contribute for TAU hyperphosphorylation, employing an omics approach to detect differentially expressed genes, metabolites and proteins, including those from the secretome.

Background: PSP is a neurodegenerative tauopathy and, to date, the pathophysiological mechanisms that lead to Tau hyperphosphorylation and neurodegeneration are not clear. The development of a model using neural cell lines derived from patients had the potential to identify molecules and possible biomarkers.
Method: Skin fibroblasts from PSP patients (without MAPT mutations) and healthy controls were reprogrammed with episomal vectors to iPSCs, which were further differentiated into neuroprogenitor cells (NPCs) and astrocytes. NPCs were checked for aneuploidies through MLPA. At the 5ht passage, astrocytes were collected for total RNA sequencing. Intracellular and secreted proteins were processed for proteomics experiments. Metabolomics profiling was obtained from supernatants only. LC and/or MS/MS systems were employed to analyze proteins or water-soluble metabolites in non-target samples. Analytical softwares or web platforms were used to process mass spectra and statistical analysis. Enriched networks were considered to describe the interactions among the biomolecules.
Results: We identified 513 differentially expressed genes. One of the main networks was related to cell cycle activation in PSP. Proteins expressed in both groups did not differ significantly, but several proteins were found exclusively in the PSP group. Of these, in the secreted proteins, we highlight the enrichment of the chaperone CTT/TriC pathway, an essential complex for cell proteostasis and axonal transport, which depends on TAU phosphorylation. Besides the exclusive proteins in the secretome and cell proteome, we found spatial segregation by PCA in the metabolomics data, indicating distinct sets of metabolites between these two groups.
Conclusion: Our iPSC-derived astrocyte model can provide distinct molecular signatures for PSP patients and is useful to elucidate the pathways of PSP progression. The CTT/TriC pathway is possibly involved in early events that lead to TAU hyperphosphorylation and shall be further explored.

LBA 4
MDS Survey of Genetic Testing and Counseling Practices for Parkinson Disease

R. Saunders-Pullman, C. Klein, M. Markgraf, S. Videmsky, R. Alcalay, V. Bonifati, SJ. Chung, T. Foroud, E. Gatto, A. Hall, N. Hattori, I. König, T. Lynch, K. Marder, D. Mascalzoni, N. Mencacci, M. Merello, I. Novakovic, G. Pal, D. Raymond, M. Salari, A. Shalash, O. Sucherowsky, C. Sue, A. Thaler, T. Simuni, The Parkinson Disease and other Movement Disorders Society Task Force for Genetic Testing in Parkinson Disease (*New York, NY, USA*)

Objective: To assess current practices, concerns, and barriers to genetic testing and counseling among the MDS membership.
Background: Prior to guideline development, the Task Force for Genetic Testing in PD identified the need to survey current practice among MDS members.
Method: 8,858 MDS members were sent a link for a 52-item multiple-choice online questionnaire querying availability and perceived barriers for genetic testing and counseling for Parkinson Disease.
Results: 568 respondents: 52% were movement specialists, 31% general neurologists, and 16% other. 11% were from Africa, 25% Asia/Oceania, 32% Europe, and 32% Pan-America. In the respondent's region, genetic testing was reported as being available only at select centers (54%), available to general neurologists (32%), and not available in their country (14%). Clinician barriers to testing (could be >1) included: cost (57%), lack availability of genetic counseling (37%), time for testing (20%), or time for counseling (17%), knowledge (14%); 8.5% indicated no barriers. Other concerns included lack of therapeutic consequences and low yield of positive tests. Major barriers clinicians perceived for patients were: cost (65%), limited knowledge about genetics (43%), lack of access to genetic counseling

(34%), lack of access separate from cost (30%). Other barriers included patients' fears of discrimination/difficulty obtaining insurance, and lack of actionable information. Type of testing included: single gene (41%), panel (53%), Whole Exome Sequencing (30%), Whole Genome Sequencing (15%). 44% reported that they were not comfortable performing genetic counseling. When performed, genetic counseling is frequently carried out by neurologists (52%), medical geneticists (30%), and genetic counselors (43%). Those in Europe, Pan-America, and Asia/Oceania had moderate access to genetic counseling, with 45%, 19%, and 29% reporting high availability, respectively, compared to 5% in Africa. Free-text comments included the need for policies and recommendations about genetic testing as well as education on genetic counseling.
Conclusion: Access to clinical genetic testing resources and availability of genetic counseling is incomplete worldwide, with availability, cost, and time serving as major barriers. Task force recommendations will need to incorporate the diversity of needs across the MDS regions. Results by region, as well as those regarding presymptomatic testing, will also be presented.

LBA 5

Delayed-start analysis of PASADENA: A randomized Phase II study to evaluate the safety and efficacy of prasinezumab in early Parkinson's disease; Part 2 Week 104 results

G. Pagano, S. Zanigni, A. Monnet, KI. Taylor, A. Hahn, K. Marek, R. Postuma, N. Pavese, F. Stocchi, T. Simuni, G. D'Urso, N. Pross, M. Lindemann, W. Zago, GG. Kinney, H. Garren, R. Tripuraneni, H. Svoboda, P. Fontoura, R. Doody, GA. Kerchner, A. Bonni, T. Nikolcheva (*Basel, Switzerland*)

Objective: To evaluate the efficacy of prasinezumab in an exploratory delayed-start analysis in individuals with early Parkinson's disease (PD) following 104 weeks of double-blind treatment.
Background: Prasinezumab is a humanised monoclonal antibody designed to target aggregated α-synuclein and slow PD progression. Prasinezumab showed a favourable safety profile and signals of efficacy on motor progression (change from baseline at Week 52 for Movement Disorder Society-Unified Parkinson's Disease Rating Scale [MDS-UPDRS] Part III score, and digital motor assessments) in the placebo-controlled Part 1 of the PASADENA (NCT03100149) Phase II study.
Method: Individuals with early PD (diagnosis ≤2 years at screening; Hoehn & Yahr Stages I–II) who were drug naïve or treated with monoamine oxidase B [MAO-B] inhibitors, were randomised to receive intravenous prasinezumab every 4 weeks (low dose or high dose) for 104 weeks (early-start group), or placebo for 52 weeks followed by prasinezumab (low dose or high dose) for 52 weeks (delayed-start group). Exploratory analyses (using Mixed Model for Repeated Measures) of change from baseline in MDS-UPDRS Part III score for early-start pooled doses vs. delayed-start pooled doses are described here. Patients contributed data until initiating dopaminergic therapy or changing MAO-B inhibitor dose ('censoring').
Results: Overall, 316 participants were recruited in the study; 309 started Part 2 and were included in this analysis. The early-start group showed a reduced change from baseline in MDS-UPDRS Part III score compared with the delayed-start group at Week 52 (early-start group: 5.02 [SE: 0.673] points vs. placebo group: 6.25 [0.911] points) and at Week 104 (early-start group: 9.18 [0.994] points vs. delayed-start group: 11.12 [1.376] points) (Figure 1). Digital motor score results were consistent with MDS-UPDRS Part III throughout the study.
Conclusion: Participants with PD who were treated with prasinezumab for 2 years in the early-start group are on a more favourable trajectory compared with participants treated with prasinezumab for 1 year in the delayed-start group. Further studies are needed to investigate these findings. The Phase IIb

PADOVA (NCT04777331) study will assess the efficacy and safety of prasinezumab in people with early PD on stable symptomatic treatment.

LBA 6

Reduction of total LRRK2 in human CSF with LRRK2 inhibitor treatment demonstrates CNS target engagement and utility of total LRRK2 as a pharmacodynamics biomarker

O. Mabrouk, R. Maciuca, J. Chen, V. Daryani, H. Wong, D. Graham, S. Huntwork-Rodriguez (*Cambridge, MA, USA*)

Objective: To measure the pharmacodynamic response of total LRRK2 (tLRRK2) in CSF to LRRK2 inhibition as an indicator of CNS target inhibition in LRRK2 inhibitor clinical studies.
Background: Phase 1 and 1b clinical studies using small molecule inhibitors of LRRK2 (BIIB122/DNL151 and DNL201) have demonstrated peripheral target engagement and safety profiles supporting continued investigation of LRRK2 inhibition with BIIB122/DNL151 for the treatment of Parkinson's disease (MDS 2021 Virtual Congress Abstract 401). A clinically translatable biomarker of LRRK2 inhibition in the brain is lacking. Recently, we published a quantitative method for measurement of tLRRK2 levels in CSF (Pubmed ID 32523511). As LRRK2 inhibition is known to reduce LRRK2 protein levels in cellular studies (Pubmed ID 27658356), we hypothesized that LRRK2 inhibition would reduce central tLRRK2 levels and that this would be reflected by a reduction in CSF tLRRK2, enabling clinical confirmation of CNS PD response.
Method: Four double-blind, placebo-controlled studies were conducted to evaluate safety, tolerability, pharmacokinetics, and PD of BIIB122/DNL151 and DNL201 in healthy subjects and Parkinson's patients: DNLI-C-0001 and DNLI-C-0003: Phase 1 and 1b studies of BIIB122/DNL151; DNLI-B-0001 and DNLI-B-0002: Phase 1 and 1b studies of DNL201. CSF was collected from subjects at baseline and on the last day of dosing (Ph1 studies: Day 10; Ph1b studies: Day 28) in a subset of dose levels (DNL151 30 mg QD – 400 mg BID; DNL201 30 mg TID – 100 mg BID) and tLRRK2 levels were quantified.
Results: BIIB122/DNL151 and DNL201 dose-dependently reduced tLRRK2 from baseline by median ~ 20 to 50% in healthy subjects and Parkinson's disease patients at doses that were generally well tolerated. At steady state, higher BIIB122/DNL151 or DNL201 CSF concentrations led to greater reduction in CSF tLRRK2 on average, demonstrating a concentration dependent PD response.
Conclusion: LRRK2 inhibition in our Ph1 and 1b studies dose- and concentration- dependently reduced LRRK2 in CSF, demonstrating CNS target engagement with BIIB122/DNL151 and DNL201 at doses expected to be clinically relevant. tLRRK2 levels in CSF will continue to be evaluated in additional LRRK2 inhibitor studies to evaluate CNS pharmacodynamic effects relative to clinical benefit.

LBA 7

CRISPR engineering of a dystonia-specific allelic series of THAP1 mutations reveals transcriptional profiles associated with myelination and neurodevelopment

A. Domingo, R. Yadav, S. Shah, W. Hendriks, S. Erdin, D. Gao, K. O'Keefe, B. Currall, J. Gusella, N. Sharma, L. Ozelius, M. Ehrlich, M. Talkowski, DC. Bragg (*Boston, MA, USA*)

Objective: To integrate disease modeling using CRISPR-modified induced pluripotent stem cells (iPSCs) with transcriptomic analyses to investigate the molecular consequences of genetic variation in THAP1.

Background: The genetic architecture of isolated dystonia is heterogeneous, and hereditary forms are associated with diverse variants in multiple genes; whether there are shared molecular pathways across mutations/genes remains uncertain. In THAP1-associated dystonia, patient-specific mutations localize to various protein domains and are thought to alter the transcriptional activity of THAP1 differently.
Method: We engineered an allelic series of eight genetic variants in a common iPSC background and differentiated these lines into a panel of near-isogenic neural stem cells (n = 94 lines). The mutant lines thus harbored one of pathogenic N12K, S21Thet/hom, P26R or C54Y mutations in the DNA-binding domain, or an R146fs in the nuclear localization sequence (NLS), an M143V variant predicted to be benign, or a deletion of the entire THAP1 coding region. These were compared to CRISPR-targeted unedited cells and untargeted iPSC lines to discover common differentially expressed genes (DEGs).
Results: Each mutation model induced significant (FDR<0.05) DEGs, with the exception of the benign variant, which behaved similar to control. Correlation of mutational profiles revealed that pathogenic variation localized to the DNA-binding domain and the NLS induce overlapping transcriptome-wide alterations (mean Spearman r = 0.56; p<0.05), including >9.6-fold enrichment for shared DEGs compared to null expectation models. Given this, we derived a joint DEG list using transcriptomic profile combination, to define the 871 genes consistently altered by mutations in these domains (FDR<0.01). Only 0.6% of these joint DEGs intersected with the DEGs induced by the deletion model, which however induced a more profound global signature of DEGs. Functional analysis across these signatures identified a convergent pattern of dysregulated genes and gene modules that are related to neurodevelopment, lysosomal lipid metabolism, and myelin. Based on these observations, we examined mice bearing Thap1-disruptive alleles (C54Y and exon-2 deletion) and detected significant changes in myelin gene expression on targeted expression assays and reduction of myelin structural integrity using staining (p<0.05).
Conclusion: Our application of a systematic experimental and analytical variant-to-function platform combining isogenic stem cell modeling with RNA-seq reveals that deficits in neurodevelopment and myelination are consequences of dystonia-specific THAP1 mutations.

LBA 8

Multicenter, randomized, double-blind, placebo controlled clinical trial with riluzole in spinocerebellar ataxia type 2

G. Coarelli, C. Fisher, ML. Monin, A. Heinzmann, C. Ewenczyk, H. Hurmic, F. Calvas, P. Calvas, C. Goizet, S. Thobois, M. Anheim, K. Nguyen, D. Devos, C. Verny, JF. Mangin, A. Brice, S. Tezenas du Montcel, A. Durr (*Paris, France*)

Objective: To measure the efficacy of riluzole in genetically homogeneous patients (SCA2) after 12 months.
Background: Two previous studies suggested clinical improvement of patients with cerebellar ataxia of various etiologies treated by riluzole.
Method: We conducted a multicenter, double-blind, placebo-controlled trial for SCA2 patients randomly assigned to riluzole (50 mg orally, twice daily) or placebo for 12 months. The inclusion criteria were SCA2 patients over 18 years old, SARA score ≥ 5 and ≤ 26, and age at onset ≤ 50 years old. Two visits were assessed, at baseline and month 12 with a neurological examination including clinical scales (SARA and INAS), a quantitative score (CCFS), quality of life questionnaire (SF-36), and brain 3T MRI. The primary endpoint was the proportion of patients with SARA score improved by at least one point. The secondary

endpoints were the change of CCFS, INAS, cerebellar and brainstem volumes. To confirm long-term clinical and biological tolerance of riluzole, blood analyses were done every 3 months.
Results: Between January 2018 and June 2019, we enrolled 45 SCA2 patients (23 in placebo and 22 in riluzole group). In placebo group, one patient dropped out due to the disease worsening. The proportion of patients with 1-point SARA score improvement was not significantly different between both groups (31.8% vs 40.9%, p=0.75), as well as the variation of SARA score at month 12 (median: 0.5 [IQR: -1.5; 2.0] vs 0.3 [-1.0; 3.0], p=0.7). CCFS worsened significantly in riluzole group (0.055 [0.014; 0,086] vs 0.004 [-0.040; 0.020], p<0.01). INAS variation was similar between treated and placebo patients (0 [-1;1] vs -1 [-2;0], p=0.07), with no improvement in motoneuronal signs. At baseline, there was a correlation between CCFS worsening and grey matter atrophy in the vermis (p=0.04). Volume loss was significant for left lobule Crus I (p=0.001) and pons (p<0.001), not significantly different in the treated group. SF-36 questionnaire did not show significant difference between groups. No significant increase in adverse events was reported in riluzole group.
Conclusion: We showed that riluzole did not improve clinical or radiological outcomes in SCA2 patients after 12 months. Interestingly, quantitative measures (CCFS) were more sensitive to change than clinical outcomes and correlated with cerebellar atrophy.

LBA 9
A data-driven model of brain atrophy progression in Progressive Supranuclear Palsy

W. Scotton, M. Bocchetta, E. Todd, N. Oxtoby, L. Vandervrede, H. Heuer, PROSPECT Consortium, 4RTNI/FTLDNI Consortia, D.C. Alexander, J.B. Rowe, H.R. Morris, A. Boxer, J.D. Rohrer, P.A. Wijeratne (*London , United Kingdom*)

Objective: The objective of this study was to characterise the progression of brain atrophy in clinically diagnosed Progressive Supranuclear Palsy (PSP) by developing an event-based model (EBM) that takes regional brain volumes extracted from cross-sectional structural MRI as input.
Background: The most common clinical phenotype of PSP is Richardson syndrome (PSP-RS), characterised by a levodopa unresponsive atypical parkinsonian syndrome with a vertical supranuclear gaze palsy, early falls, and dementia. Clinical trials in PSP are complicated by disease heterogeneity, with no clear objective biomarkers to stratify patients into homogeneous cohorts based on disease stage. Reliable and individualised disease progression markers are therefore urgently needed. Determining the sequence of brain atrophy in PSP-RS could provide important insights into disease progression and guide patient stratification for clinical trials.
Method: We determine the probabilistic sequence of brain atrophy in clinically diagnosed PSP-RS using a data-driven approach: the event-based model (EBM). Model stage is determined for each MRI scan by finding the best match between the atrophy snapshot of the MRI and the cumulative atrophy stage of the EBM. We assembled a large international cohort of 341 PSP-RS cases (255 had 12-month follow-up scans) and 260 age and gender matched controls. The EBM was fit using volumetric MRI features extracted from baseline structural (T1-weighted) MRI scans and validated using a combination of 12-month follow-up MRI data, and a clinical rating score (PSP rating scale) to demonstrate the longitudinal consistency and utility of the EBM's fine-grained staging system.
Results: The EBM estimated that the earliest atrophy occurs in the brainstem and subcortical regions followed by progression caudally into the superior cerebellar peduncle and deep cerebellar nuclei, and rostrally to the cortex. The sequence of cortical atrophy progresses in an anterior to posterior direction, beginning in the frontal lobe before then spreading to the temporal, parietal and finally the occipital

lobe. This ordering was robust under bootstrap cross-validation of the uncertainty in the sequence. Using longitudinal information from 12- month follow-up scans, we confirmed the validity of the model, with cases consistently moving to later stages over this time interval. EBM stage correlated ($p<0.01$) with a validated measure of clinical disease severity (PSP rating scale).
Conclusion: We used a probabilistic data-driven method applied to cross-sectional structural MRI to characterise the most likely sequence in which brain regions become atrophic in PSP-RS. The pattern of regional atrophy progression predicted in vivo by the EBM broadly mirrors the sequential spread of tau pathology proposed by Kovacs et al. postmortem. The EBM can stage individuals at baseline, with implications for screening on entry into clinical trials, to improve cohort homogeneity and increase the power to detect a treatment effect.

LBA 10

SAGE-324/BIIB124, an oral neuroactive steroid (NAS) GABA-A receptor positive allosteric modulator (PAM), in patients with essential tremor: results from the phase 2 KINETIC trial

K. Bankole, K. Takahashi, M. Qin, H. Colquhoun, RJ. Elble (*Cambridge, MA, USA*)

Objective: To present efficacy, safety, and tolerability from the phase 2, placebo-controlled KINETIC Study (NCT04305275) of SAGE-324/BIIB124 60 mg in patients with essential tremor (ET) aged 18 to 80 years.
Background: SAGE-324/BIIB124 is an investigational, oral neuroactive steroid (NAS) gamma-aminobutyric acid type A (GABA-A) receptor positive allosteric modulator (PAM). GABA dysregulation has been implicated in the pathophysiology of ET.
Method: Patients with ET (N=69), ages 18–80 years, with a score of ≥10 on item 4 (upper limb tremor score) of The Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale at screening and baseline were randomized 1:1 to receive SAGE-324 60 mg or placebo once daily for 28 days. SAGE-324 could be down-titrated to 45 mg or 30 mg based on clinical judgement and tolerability. The primary endpoint was change from baseline compared to placebo in TETRAS item 4 at Day 29 (1 day after last dose).
Results: Sixty-nine patients were randomized to receive SAGE-324 60 mg (n=34) or placebo (n=35). Of the 34 patients randomized to SAGE-324, 23.5% (8/34) completed the treatment period on the 60 mg dose, 55.9% (19/34) had their dose reduced to 45 mg, 32.4% (11/34) had their dose further reduced from 45 mg to 30 mg, and 5.9% (2/34) had their dose reduced from 60 mg directly to 30 mg. Patients who received SAGE-324 experienced a statistically significant least-squared (LS) mean [SE] reduction from baseline at Day 29 in TETRAS item 4 (SAGE-324: -2.31 [0.401]; placebo: -1.24 [0.349]; p=0.049), corresponding to a 36% reduction from baseline in tremor amplitude compared to a 21% reduction in patients who received placebo. Patients with a baseline TETRAS item 4 score at or above the median score of 12 (SAGE-324: n= 25; placebo: n=22) also experienced a significant LS mean [SE] reduction from baseline (SAGE-324: -2.75 [0.426]; placebo: -1.05 [0.412]; p=0.007), corresponding to a 41% reduction from baseline in tremor amplitude in patients who received SAGE-324 compared to an 18% reduction in patients who received placebo. The most common TEAEs occurring in ≥10% of patients in the SAGE-324 treatment group and at a rate at least twice that of placebo were somnolence 67.6%, dizziness 38.2%, balance disorder 14.7%, diplopia 11.8%, dysarthria 11.8%, and gait disturbance 11.8%.
Conclusion: SAGE-324 treatment led to a significant reduction in upper limb tremor at Day 29 compared with placebo.

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Deterministic tractography-based versus indirect-targeting magnetic resonance-guided focused ultrasound treatment of medication-refractory essential tremor: 3-year results of a prospective cohort study

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Objective: To compare long-term outcomes of tractography-based and indirect-targeting magnetic resonance-guided focused ultrasound thalamotomy (MRgFUS) in medication-refractory essential tremor (ET).
Background: Successful MRgFUS for ET requires precise targeting of the thalamic ventrointermediate (VIM) nucleus. Diffusion tensor imaging (DTI)-tractography localises VIM more accurately than standard indirect-targeting, yet outcome comparisons are sparse. We prospectively evaluated deterministic tractography-based targeting and indirect-targeting MRgFUS outcomes in medication-refractory ET over 3 years.
Method: 136 ET patients refractory to ≥3 medications with significant dominant-hand tremor were included (2 centres). 58 received tractography-based MRgFUS. 78 received indirect-targeting MRgFUS. All tractography-based patients underwent pre-treatment 3T MRI, 3-tract deterministic DTI-tractography (targeting dentatorubrothalamic, pyramidal and somatosensory tracts) for contralateral VIM localisation (Brainlab iPlan), and indirect-targeting for VIM location comparison, before tractography-based direct-targeting MRgFUS. Indirect-targeting patient outcomes were correlated with overlap between MRgFUS-lesion and tractographic region-of-interest derived retrospectively from pre-treatment DTI (Spearman's rank). Total and hand tremor (Clinical Rating Scale for Tremor [CRST] total and A+B subscores) and adverse events (AE) were compared 3-monthly for 3 years.
Results: Mean CRST total and A+B scores improved post-MRgFUS from similar baselines in both groups (3-year: tractography -38.9,-12.8; indirect-targeting -30.6,-10.0, $p<0.0001$). Tractography-group had significantly-greater improvements at all timepoints (3-year mean change from baseline intergroup difference: CRST -6.2, $p<0.0001$; CRST-A+B -1.4, $p=0.0015$) (Tables 1, 2). Anteroposterior coordinate in tractography-group differed significantly from that generated by indirect-targeting (7.7±0.8 vs 6.3±0.2mm, $p<0.001$). In indirect-targeting group, region-of-interest and lesion overlap correlated with greater CRST percentage-reduction ($r=-0.732,-0.768,-0.814$ at 1, 2, 3 years,$p<0.03$). Tractography-group had lower AE rate (29.8% vs 47.4%) and quicker recovery for post-MRgFUS ataxia (1.2 vs 3.5months, $p=0.03$).
Conclusion: In the largest prospective comparative study, tractography-based MRgFUS demonstrates superior long-term efficacy, VIM-targeting accuracy and reduced AE incidence over indirect-targeting MRgFUS for medication-refractory ET.

Table 2: Outcomes in tractography-based targeting versus indirect-targeting MRgFUS for essential tremor- Treated hand tremor (CRST A+B subtotal scores)

CRST A+B subscore	Tractography group ($n = 58$) Mean ± SD Mean change from baseline, intra-group p value compared to baseline (n at each timepoint)	Indirect-targeting group ($n = 78$) Mean ± SD Mean change from baseline, intra-group p value compared to baseline (n at each timepoint)	Inter-group difference in mean change from baseline (95% CI)	Inter-group p value
Baseline	19.8±6.5 ($n = 58$)	18.4±6.9 ($n = 78$)		$p = 0.2325$
3 months	6.1±3.1 -13.7, $p<0.0001$ ($n = 58$)	7.9±3.2 -10.5, $p<0.0001$ ($n = 73$)	-1.8 (-2.90, -0.70)	$p = 0.0015$
6 months	5.6±2.2 -14.2, $p<0.0001$ ($n = 58$)	8.1±2.8 -10.3, $p<0.0001$ ($n = 71$)	-2.5 (-3.39, -1.61)	$p < 0.0001$
Year 1	6.9±2.3 -12.9, $p<0.0001$ ($n = 54$)	9.2±3.6 -9.2, $p<0.0001$ ($n = 68$)	-2.3 (-3.42, -1.18)	$p < 0.0001$
Year 2	7.4±3.0 -12.4, $p<0.0001$ ($n = 52$)	8.8±3.5 -9.6, $p<0.0001$ ($n = 62$)	-1.4 (-2.62, -0.18)	$p = 0.0252$
Year 3	7.0±2.1 -12.8, $p<0.0001$ ($n = 47$)	8.4±2.3 -10.0, $p<0.0001$ ($n = 62$)	-1.4 (-2.25, -0.55)	$p = 0.0015$

CI, confidence interval; SD, standard deviation.