Medicom International Conference Series in Neurology

AAN 2022 Annual Meeting

American Academy of Neurology

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PEER-REVIEWED CONFERENCE REPORT

Gene Therapy Efficacious in Spinal Muscular Atrophy

Onasemnogene abeparvovec was efficacious in patients with spinal muscular atrophy (SMA) aged 6 months or older, according to the latest results of the observational RESTORE study.

read more on PAGE 13

IPX203 Versus Immediate Release Carbidopa-Levodopa

IPX203, an investigational oral extended-release formulation of carbidopa-levodopa, resulted in an improvement in "good on" time of patients with Parkinson's disease, while requiring fewer daily dosages.

read more on PAGE 18

Long-Term Consequences of COVID-19

COVID-19 survivors displayed neurological alterations 2 months after hospital discharge, but improvements at 10 months. Dysgeusia and hyposmia during acute COVID-19 were related to vulnerability of memory over time.

read more on PAGE 19

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Letter from the Editor

Dear colleagues,

A meeting in person again – this was the first news from this year's AAN meeting that took place in Seattle. The meeting in hybrid format attracted some 8000 neurologists participating in situ and many who followed the attractive program online. All colleagues in Seattle enjoyed meeting old and making new friends during a week of densely packed educative and scientific sessions that covered beyond science all aspects of neurology practised in private office, hospital, or academic settings.

This review aims at providing summaries of the essentials of varied topics covered in the scientific sessions.

Alzheimer disease, the controversy around the monoclonal antibody aducanumab and many new therapeutic strategies, and COVID-19 were covered each day. The encouraging progress in some of the most devastating inherited diseases capitalising on technological platforms to rectify genetical aberrations of neuromuscular and CNS disorders ranging from spinal muscular atrophies to Huntington and Parkinson disease (oligonucleotide antisense and viral vector approaches) was presented. So were studies on the SARS-CoV-2 pandemic and its neurological consequences, from clinical descriptions, outcomes, the long haul COVID-19 manifestations, and pathology, to concepts of its pathogenesis and new therapies.

I sincerely hope you will get an idea of the breadth of scientific and management progress in the many diseases affecting the nervous system reviewed here.

Please enjoy the reading.
Hans-Peter Hartung

Biography

Prof. Hartung is currently Professor of Neurology at Heinrich-Heine-University Düsseldorf, Honorary Professor at Brain and Mind Center, University of Sydney, Visiting Professor at Medical University Vienna and Palacky University Olomouc. He was chairman of the Department of Neurology, Heinrich-Heine-University Düsseldorf from 2001-2020, director of the Center for Neurology and Neuropsychiatry from 2012-2020 and director of the Department of Conservative Medicine from 2012-2019.

Prof. Hartung's clinical and translational research interests are in the field of basic and clinical neuroimmunology and in particular multiple sclerosis and immune neuropathies, development of new immunological, neuroprotective and neural repair promoting strategies. He has (co-)authored more than 950 articles in peer-reviewed journals and 100 book chapters. He has been involved as member of the Steering Committee in numerous international multicentre therapeutic phase 2 and 3 trials in multiple sclerosis, Guillain-Barré Syndrome and CIDP.

He was President of ECTRIMS and has served/serves amongst others on the executive boards of the European Charcot Foundation, the European Neurological Society, and the International Multiple Sclerosis Cognition Society (IMSCOGS). He is/was also member of the Editorial Board of a number of international journals. Prof. Hartung is a Fellow of the AAN and EAN, and has been chair/member of the management group of the EAN scientific panels on general neurology and multiple sclerosis. He is Corresponding and Honorary Fellow of several international societies.

Conflict of Interest Statement:
Hans-Peter Hartung has received fees for consulting, speaking, and serving on steering committees from Bayer Healthcare, Biogen, GeNeuro, MedImmune, Merck, Novartis, Opexa, Receptos Celgene, Roche, Sanofi Genzyme, CSL Behring, Octapharma, Teva, TG Therapeutics, and Viela Bio, with approval by the Rector of Heinrich-Heine University.

"We decided to create unique experiences for both in-person and virtual attendants"

Interview with
Prof. Natalia Rost, MD, MPH, FAHA, FAAN,
chair of the Science Committee of the 2022 AAN meeting

Prof. Natalia Rost is Chief of the Stroke Division at Massachusetts General Hospital and Professor of Neurology at Harvard Medical School. As chair of the Science Committee, Prof. Rost was interviewed by Medicom about the exceptional way this year's AAN annual meeting was organised and mentioned some of the highlights of the hybrid meeting in Seattle.

How was it to have an in-person meeting again after a 3-year absence?

"This was a glorious experience. There was joy in the air, palpable to those who were there. Even the masks did not deter us from smiling all the time. After such a long break, it was a much-needed experience."

How many attendants were in Seattle, and how many more participated online?

"This was almost a week-long meeting, so we had waves of people coming and going, swelling up to a maximum at the middle of the week of of over 7,000 people on site."

Effectively, there were 2 AAN annual meetings in 2022.

"We had 2 separate meetings: one was in person in Seattle, on April 2–7, with access to online material on demand a few weeks later. And then there was a stand-alone virtual meeting, on April 24–26."

That is a rather original approach to organise an annual meeting.

"The AAN is one of the more creative organisations of its kind and likes to be innovative in approaching formats. This meeting was no exception. We spent a lot of time deciding how to reconcile certain limitations of an in-person meeting and some of the unique aspects of a virtual meeting that cannot be fully replicated when you attend in person. Take the so-called fireside chats, which are very different in person compared with virtual. So rather than offering a less than optimal experience to those unable to join in person, or who prefer a virtual format, we decided to create unique experiences for both in-person and virtual attendants, focusing on the advantageous aspects that both formats have. We went to great lengths to offer original content for the virtual meeting, including original scientific research, in addition to to highlights of the in-person meeting, such as award-winning lectures and other plenary presentations. It was a unique experience."

Do you think this particular experience and set-up of the AAN annual meeting will be repeated in the next few years?

"Going forward and pandemic permitting, we will continue to reinvent what getting together looks like. The virtual conferencing is here to stay; an *annual* virtual meeting however, is not necessarily required. This year, almost 4,000 people chose —for different reasons— to solely attend the second, virtual meeting. So we need to continue to think about what we can offer to them in the future. Anyhow, virtual education is here to stay."

This conference report covers the in-person meeting in Seattle. As a stroke specialist, what presentation(s) specifically drew your attention?

"There was a great showing of neurovascular science. For me personally, some plenary presentations stood out. My favourites were the 2 presentations at the presidential plenary session. Prof. Bruce Ovbiagele from the University of California in San Francisco gave a fantastic lecture on global health disparities in cerebrovascular care and on the need to include individuals of every background in stroke research to develop treatments applicable across the world. I also greatly enjoyed the lecture by Prof. Dr Catherine M. Amlie-Lefond, winner of the Sidney Carter Award in Child Neurology, who spoke on pediatric stroke. It was an intriguing, clinically-centred talk on this rare disease and its management, that deserves greater attention. At the Emerging Science session, there was a fascinating talk on an endovascular brain-computer interface, which helped ALS patients to operate a computer. I hope that at some point it can help the rehabilitation science in stroke to move forward too."

What else would you consider to be a highlight of the 2022 AAN meeting?

"One thing I would like to mention is the amyloid therapies that are emerging. True, the first amyloid-removing therapy, aducanumab, came to the market surrounded by controversy. But what I found striking were the clinical trial results on other emerging new-generation amyloid therapies. Preliminary data on donanemab for example showed that it not only removes amyloid but also decreases phosphorylated (P)-tau217 and glial fibrillary acidic protein (GFAP), biomarkers of neurodegeneration. Another one was lucanumab, of which phase 2 results were presented. And then there is SAGE-718, which modulates the N-methyl-D-aspartate (NMDA) receptor. The race is on in neurodegenerative diseases, especially Alzheimer's."

Alzheimer's Disease and Other Dementias

Targeting senescent cells to treat age-related diseases

How to target ageing? It might be done by clearing the brain of senescent cells. Senolytics, including the combination of dasatinib plus quercetin, are therapeutic agents that can induce the death of senescent cells. The phase 2 StoMP-AD trial is now enrolling participants to investigate this hypothesis in the treatment of Alzheimer's disease (AD).

Dr Miranda Orr's (Wake Forest School of Medicine, NC, USA) research focuses on the molecular mechanisms of AD and the effects of tau accumulation on cellular senescence and the risk of chronic neurodegenerative diseases. Decades prior to clinical symptoms of AD, changes already occur in the brain. Understanding these fundamental processes could lead to them being targeted, potentially slowing down the process of ageing in the entire organism, which is the greatest risk factor for developing AD and other chronic diseases. This is the so-called geroscience approach. Dr Orr explained: "As older adults age, they very rarely suffer from only one problem. Older adults with AD suffer from more comorbidities than age-matched older adults without dementia."

Senescent cells are a possible target for ageing, according to Dr Orr [1,2]. Senescent cells are old, stressed, or damaged and do not function properly anymore, but they do not die either [3]. Instead, they can secrete factors that cause inflammation and dysfunction—a senescence-associated secretory phenotype (SASP)—causing damage to adjacent healthy cells [4]. Moreover, when microglia engulf senescent neurons, the microglia become senescent themselves [5]. They become dysfunctional and start to secrete molecules that are highly toxic to neurons.

The discovery of a SASP and other cellular senescence biomarkers *in vitro* has led to the identification of cellular senescence *in vivo*. In 2002, cell senescence was detected in human atherogenic plaques; in 2006, in primate skin; and in 2011, clearing senescent cells was found to ameliorate progeroid phenotype, preventing or delaying tissue dysfunction and extending the healthspan in a mouse model [6–8]. Cellular senescence is strongly associated with the presence of tau-containing neurofibrillary tangles (NFT) [5]. The accumulation of NFT is the closest correlate with cognitive decline and cell loss in AD.

"Let's help the brain clear senescent cells," proposed Dr Orr. "Senolytics are therapeutic agents that can do this." Senolytics transiently disable the pathways that defend senescent cells against their own apoptotic environment. Intermittent administration of the combination of dasatinib and quercetin was proven to selectively eliminate senescent cells from mouse and human cell cultures, and to improve clinically relevant outcomes in multiple animal models [9]. Dasatinib plus quercetin demonstrated to be safe and well tolerated in humans and reduced senescence-associated inflammatory markers in a small, open-label pilot study on 5 older adults with early-stage AD, thus supporting phase 2 testing, according to Dr Orr [10].

The placebo-controlled, phase 2 StoMP-AD trial (NCT04685590), set up by Dr Orr's group, is now enrolling participants. Dasatinib plus quercetin will be administered once daily for 2 consecutive days, followed by a 13-day (± 2 days) no-drug period, for 12 consecutive weeks. This intermittent dosing phase will be followed by 9 months of follow-up to observe if senescent cells return. The outcome measures will be the incidence of Adverse Events and Serious Adverse Events between treatment and placebo. Dr Orr added that many other trials targeting senescent cells—in other organs than the brain—are underway for different age-associated phenotypes.

1. Orr ME. Therapeutically Targeting Senescent Cells to Treat Age-related Diseases. Hot Topics Session, AAN 2022, 02–07 April, Seattle, USA.
2. Gonzales MM, et al. Mech Ageing Dev. 2021;200:111589.
3. Gorgoulis V, et al. Cell. 2019;179(4):813–827.
4. Shenghui H & Sharpless NE. Cell. 2017;169(6):1000–1011.
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6. Minamino T, et al. Circulation. 2002;105(13):1541–4.
7. Herbig U, et al. Science. 2006;311(5765):1257.
8. Baker DJ, et al. Nature. 2011;479(7372):232–6.
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Cardiorespiratory fitness protects against dementia

In a large, prospective study, high cardiorespiratory fitness lowered the risk of developing Alzheimer's disease (AD) and related disorders (ADRD). The association was inverse, independent, and graded: the highest-fit group had the lowest ADRD risk, the lowest-fit group the highest.

Cardiorespiratory fitness is associated with favourable health outcomes, but the impact on the risk of incident AD/ADRD is

unknown [1]. This relationship was examined in 649,605 military veterans in the Veterans Health Administration database who completed a standardised exercise treadmill test between 2000 and 2017 and did not have ADRD at that time [2]. Participants were aged between 30 and 95 years (average age: 61 years); 5.7% were women and 16.6% African Americans. Based on peak metabolic equivalents (METs) during the first exercise treadmill test, they were differentiated into 5 age-specific fitness categories: lowest-fit (n=132,634; METs=3.8), low-fit (n=129,493; METs=5.8), moderate-fit (n=120,988; METs=7.5), fit (n=137,122; METs=9.2), and highest-fit (n=129,368, METs=11.7). The lowest-fit group was the reference to establishing hazard ratios for incident ADRD. The average follow-up was 8.8 years.

The results showed a strong, graded, inverse association between cardiorespiratory fitness and ADRD risk. Incident rates for ADRD were 9.5, 8.5, 7.4, 7.2 and 6.4 per 1,000 person-years in the low-fit, moderate-fit, high-fit, and highest-fit group, respectively (P<0.001). The adjusted HR for incident ADRD in respectively the lowest-fit to the highest-fit group were 0.87 (95% CI 0.85–0.90; P<0.001), 0.80 (95% CI 0.78–0.83; P<0.001), 0.74 (95% CI 0.72–0.76; P<0.001), and 0.67 (95% CI 0.65–0.70; P<0.001), respectively, compared with the lowest-fit group. A limitation of the study was that most participants were men and white.

"One exciting finding of this study is that as people's fitness improved, their risk of AD decreased – it was not an all-or-nothing proposition," said study author Dr Edward Zamrini (Washington DC VA Medical Center, DC, USA). "So people can work towards making incremental changes and improvements in their physical fitness, which will then hopefully be associated with a related decrease in their future risk of AD."

1. Rolland Y, et al. Clin Geriatr Med. 2010;26(1):75–87.
2. Zamrini E, et al. Cardiorespiratory fitness is protective against Alzheimer's and related disorders. S15.008, AAN 2022, 02–07 April, Seattle, USA.

Safety and effects of bosutinib in Lewy body dementia

A phase 2 study assessed the safety pharmacokinetics and biomarker effects of 12-week oral treatment with bosutinib in dementia with Lewy bodies (DLB). Bosutinib 100 mg inhibited Abl/Src in plasma, reduced brain alpha-synuclein, and improved activities of daily living. These outcomes will guide adequately powered larger studies in DLB.

Bosutinib is a dual Abl/Src tyrosine kinase inhibitor which is already approved at a daily oral dose of 400–600 mg for the treatment of chronic myeloid leukaemia (CML), with manageable side effects [1,2]. In preclinical studies, bosutinib (1–10 mg/kg) reduced neuropathological processes, including accumulation of neurotoxic proteins [3]. Bosutinib also increased brain dopamine levels (by >60%) in models of alpha-synuclein-opathies [4]. Bosutinib has been shown to penetrate the brain, promote autophagic degradation of neurotoxic proteins, and improve motor and cognitive behaviour in Alzheimer's disease (AD) and Parkinson's disease (PD) models [5].

Dr Fernando Pagán (Georgetown University Hospital, DC, USA) and colleagues evaluated the safety and pharmacokinetics of 12-week oral treatment of bosutinib 100 mg [6]. Their single-centre, double-blind, placebo-controlled, phase 2 study enrolled 26 patients (25 male) with mild-to-moderate DLB. Average age of participants was 73 years. Randomisation was preceded by an open-label pharmacokinetics study, in which the 26 participants were randomised to a single dose of bosutinib 100 mg, 200 mg, or placebo. Both single doses of bosutinib resulted in a dose-dependent increase in plasma and CSF bosutinib levels.

The most important observation in the main study was that multiple dosing (during 12 weeks) of 100 mg bosutinib resulted in a dose-dependent effect: a more than 2-fold elevation in plasma and 9-fold elevation in CSF. The volume of distribution was large, suggesting that bosutinib was distributed extensively into tissues with low bioavailability. Bosutinib also exhibited high protein binding of 94%.

Bosutinib achieved a sufficiently high level to directly inhibit both Abl and Src in plasma, indicating dual target engagement. Bosutinib inhibited Abl/Src at IC_{50}=1.2 nM. Bosutinib significantly reduced CSF alpha-synuclein (P=0.023) and the ratio of oligomeric/total alpha-synuclein (P=0.045) compared with placebo. Plasma oligomeric alpha-synuclein (P=0.04) and ptau181/Aβ42 (P=0.03) also significantly decreased. Finally, bosutinib significantly (P=0.034) improved activities of daily living (ADCS-ADL-MCI). There were no serious adverse events.

These results suggest that bosutinib 100 mg may be (or nearly be) the lowest effective dose to inhibit CSF Abl in DLB. More adequately powered studies are needed to further explore the effects of bosutinib.

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2. Khoury HJ, et al. Blood. 2012;119(15):3403–12.
3. Boschelli F, et al. Eur J Cancer. 2010;46(10):1781–9.
4. Lonskaya I, et al. EMBO Mol Med. 2013;5(8):1247–62.
5. Hebron ML, et al. Autophagy. 2013;9(8):1249–50.
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Epilepsy

"Women with epilepsy should be encouraged to breastfeed"

Additional evidence from the MONEAD study supports the choice of breastfeeding by women on anti-seizure medication (ASM). Focusing on some of the newer ASMs, results showed that neurodevelopmental outcomes at the age of 3 did not differ in children of women with epilepsy who breastfed compared with those who did not.

Potential adverse neurodevelopmental effects of ASM exposure via breastfeeding have so far only been directly compared in 2 prior studies that involved mostly older ASMs [1,2]. Prof. Kimford Meador (Stanford Comprehensive Epilepsy Center, CA, USA) presented the results of the ongoing, observational, prospective MONEAD study (NCT01730170) [3].

The study cohort consisted of 258 children whose mothers had used 1 (79%) or more (21%) ASMs during the third trimester of their pregnancy, of whom 195 were breastfed and 63 were not. The most frequently used ASMs were lamotrigine (35%), levetiracetam (28%), or both (10%). The primary outcome was a verbal index score at age 3, calculated by averaging the following scores: Differential Ability Scales-II (DAS-II) Naming Vocabulary and Verbal Comprehension subtests, Preschool Language Scale-5 Expressive Communication and Auditory Comprehension subscales, and Peabody Picture Vocabulary Test-4.

No difference was detected in neurodevelopmental outcomes at age 3. Adjusted verbal index score (least square means) was 103 in children of women with epilepsy and 102 in children of healthy women (P=0.770). Breastfeeding did not have any impact on cognitive outcomes either. The adjusted verbal index score was 103.3 for children of women with epilepsy who were breastfed versus 100.6 for those who were not (P=0.108).

"This is a very positive message for women with epilepsy," said Prof. Meador. Despite high ASM concentrations in blood samples of breastfeeding women, no high ASM concentrations were observed in blood samples of children who were breastfed, possibly due to the high metabolism rate of infants. This might explain why these children were not affected by ASM use of their mothers. Prof. Meador concluded: "Given the known multiple benefits of breastfeeding for the infant and mother from general population data, women with epilepsy should be encouraged to breastfeed."

Dr Jennifer Hopp (University of Maryland School of Medicine, MD, USA) commented on the results and told the audience: "Help these women make informed decisions. These results support the choice to breastfeed while using some of the newer ASMs. The next step is yours." The MONEAD study will continue to follow the children until the age of 6 years.

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2. Wiggs KK, et al. Neurology. 2020;95(24):e3232–40.
3. Meador K, et al. Breastfeeding with antiseizure medications: Effects on neuropsychological outcomes at Age 3 years in the MONEAD Study. Contemporary Clinical Issues, AAN 2022, 02–07 April, Seattle, USA.

Fenfluramine: possible new treatment for Lennox-Gastaut syndrome

Fenfluramine was associated with a sustained reduction in frequency of seizures resulting in drops for up to a year in patients with Lennox-Gastaut syndrome (LGS) in the open-label extension (OLE) of a phase 3 study. The novel treatment was generally well tolerated.

Fenfluramine (3-trifluoromethyl-N-ethylamphetamine) is a substituted amphetamine that is structurally similar to serotonin. It is thought to reduce seizures by acting as an agonist of specific serotonin receptors in the brain, including 5-HT1D, 5-HT2A, and 5-HT2C. Fenfluramine is used to treat seizures in patients with Dravet syndrome [1]. At the AAN 2022 meeting, an interim analysis of long-term safety and efficacy of fenfluramine in patients with LGS was presented. Dr Kelly Knupp (Children's Hospital Colorado, CO, USA) shared the results of the OLE (NCT03355209) of the randomised-controlled, phase 3 trial [2]. The results were published in *JAMA Neurology* [3].

In this study, fenfluramine 0.7 mg/kg/day given for 14 weeks led to a median reduction in seizures of 26.5%, while the reduction in the placebo group was 7.6% (estimated median difference -19.9%; P=0.0013).

At data cut-off for this interim analysis (19 October 2020), 247 patients participated in the OLE. Mean age was 14.3 years, a third were adults. They all started on fenfluramine at 0.2 mg/kg/day and were titrated to effectiveness/tolerability after 1 month.

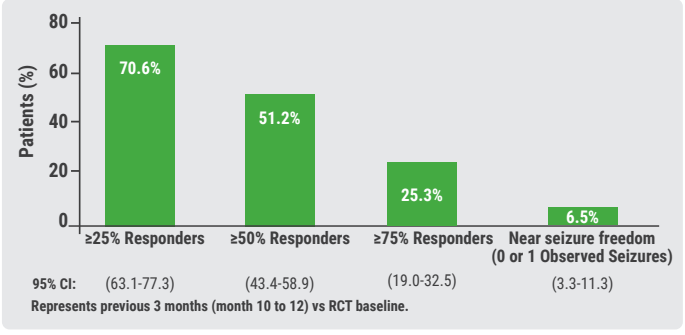
The 5 most common concomitant anti-seizure medications (ASMs) were valproate, clobazam, lamotrigine, levetiracetam, and rufinamide; 88.3% of patients received 2-4 concomitant ASMs.

After 3 months, patients experienced sustained clinically meaningful reduction in median frequency of seizures associated with a drop ("drop seizures") between 39.4%–51.8%. This treatment effect of fenfluramine was sustained up to 12 months. A statistically significant change in median frequency of seizure subtypes from pre-randomisation baseline was observed after 1 year of treatment in the OLE:

- generalised tonic-clonic: -62.8%;
- tonic: -60.4%;
- atonic: -67.4%;
- tonic-atonic: -50.8%.

A total of 87 patients (51.2%) experienced ≥50% reduction in drop seizure frequency (see Figure). About half of the investigators and caregivers rated patients as much improved/very much improved. Dr Knupp added that fenfluramine was generally well tolerated. The 2 most frequent treatment-emergent adverse events were decreased appetite (16.2%) and fatigue (13.4%). No case of valvular heart disease or pulmonary arterial hypertension was observed during the OLE. Dr Knupp concluded: "Fenfluramine may be an important new treatment option with a novel mechanism of action for patients with LGS."

Figure: Responder rates for drop seizures in patients with LGS treated with fenfluramine at ~1 year [2]



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3. Knupp KG, et al. JAMA Neurol, May 02, 2022. DOI:10.1001/jamaneurol.2022.0829.

Laser interstitial thermal therapy for refractory epilepsy

In 2 presentations at the AAN 2022, laser interstitial thermal therapy (LITT) was evaluated as an upcoming, minimally-invasive treatment option for refractory epilepsy. LITT was found to be safe in carefully selected patients. Careful management of post-operative seizures and discharge planning after epilepsy surgery may be important to optimise outcomes and reduce the risk of readmission.

A first study reported the trends and outcomes in the USA after surgical procedures for refractory epilepsy [1]. LITT has the advantage of being minimally invasive and is increasingly used for different brain lesions, offering seizure outcomes comparable with those of more traditional open surgery. In order to compare LITT to other procedures, all adult refractory epilepsy patients in the Nationwide Readmission Database were included who had either open surgery or LITT and were then readmitted within a month after discharge between 2012 and 2018.

Of 205,966 patients with refractory epilepsy, 3.1% (n=7,950) underwent either LITT (7.6%) or an open-surgical procedure (92.4%) which included lobectomy, partial lobectomy, or amygdalohippocampectomy. LITT was associated with a shorter hospital stay, a higher likelihood of being discharged, lower readmission rate, and lower costs. In the LITT group, 6.3% were readmitted to hospital within 30 days, this was 9.2% in the open-surgery group. Median length of stay after readmission was 1 day and 4 days, respectively. Incidence of post-operative infections was 13% versus 26.5% (CNS infection 3.0% vs 5.2%), and incidence of disposition to facility was 2.4% versus 7.9%. A higher rate of uncontrolled epilepsy-related readmission was present in patients treated with LITT (47.8% vs 27.1%) and LITT had a lower treatment response rate (7.6% vs 92.4%).

In another analysis with data from the Nationwide Readmission Database, about 1 in 10 RE patients who underwent LITT between 2010 and 2018 were readmitted within 30 days of discharge [2]. The most common reasons were persistent epilepsy (24.8%) and post-operative infections (22.6%). The incidence of post-operative blood transfusion, CNS infections and CNS complications was higher in patients who were readmitted.

Prof. Varun Kumar (Icahn School of Medicine at Mount Sinai, NY, USA) concluded that in carefully selected refractory epilepsy patients, LITT is a relatively safe treatment option [1]. Careful management of post-operative seizures and discharge planning after epilepsy surgery may further optimise outcomes and reduce the risk of readmission for these patients [1,2].

1. Kumar V, et al. Comparison of nationwide trends in 30-day readmission rates after laser interstitial thermal therapy (LITT) and open surgical procedures for refractory epilepsy (Nationwide Readmission database 2012-2018). S24.004, AAN 2022, 02–07 April, Seattle, USA.
2. Kumar V, et al. Outcomes and Resource Utilization Associated with Readmissions after laser interstitial thermal therapy for refractory epilepsy: A Nationwide Readmission database study (2010-2018). S24.007, AAN 2022, 02–07 April, Seattle, USA.

Migraine

Migraine may be an important obstetric risk factor

In a large study evaluating over 30,000 pregnancies between 1989 and 2009, pre-pregnancy migraine had a higher risk of pre-term delivery, gestational hypertension, and pre-eclampsia. Migraine history and phenotype may be important considerations in obstetric risk assessment and management.

Migraine and adverse pregnancy outcomes share a common pathophysiology [1]. "Roughly 20% of women of childbearing age experience migraine, but the impact of migraine on pregnancy outcomes has not been well understood," said study author Dr Alexandra Purdue-Smithe (Harvard Medical School, MA, USA) [2]. This is due to a lack of large prospective studies. Her group in Boston used data from 30,555 pregnancies in 19,694 participants of the longitudinal Nurses' Health Study 2 and estimated associations of confirmed migraine before pregnancy with pre-term delivery (<37 weeks), gestational diabetes mellitus (GDM), gestational hypertension, pre-eclampsia, and low birthweight (<5.5 lbs).

Pre-pregnancy migraine was found in 11% of participants. Compared with women without migraine, they had a 17% higher risk of pre-term delivery (RR 1.17; 95% CI 1.05–1.30), a 28% higher risk of gestational hypertension (RR 1.28; 95% CI 1.11–1.48), and a 40% higher risk of pre-eclampsia (RR 1.40; 95% CI 1.19–1.65). Pre-pregnancy migraine was not associated with low birth weight (RR 0.99; 95% CI 0.85–1.16) or GDM (RR 1.05; 95% CI 0.91–1.22). Migraine with aura may be more strongly associated with pre-eclampsia, as the risk of pre-eclampsia was 51% higher (RR 1.51; 95% CI 1.22–1.88) among migraine patients with aura, and 29% higher among migraine patients without aura (RR 1.29; 95% CI 1.04–1.61), when compared with women without migraine. Aspirin use was associated with a lower risk of adverse pregnancy outcomes among women with migraine.

These associations may overall not be very strong, but women with a history of migraine should be aware of potential pregnancy risks, according to Dr Purdue-Smithe. "Women with migraine may benefit from closer monitoring during pregnancy, so that complications like pre-eclampsia can be identified and managed as soon as possible."

1. Aukes AM, et al. Obstet Gynecol Surv. 2019;74(12):738–748.
2. Purdue-Smithe A, et al. Pre-pregnancy migraine and risk of adverse pregnancy outcomes. S4.003, AAN 2022, 02–07 April, Seattle, USA.

Intranasal zavegepant safe and well tolerated in healthy adults

Intranasal zavegepant is in development for the acute treatment of migraine. Escalated to 40 mg/day for up to 14 days, it was safe and well tolerated in healthy adults in 2 sequential phase 1 studies. Doses of ≥10 mg produced exposure that is assumed to be efficacious in adults with migraine.

For acute treatment of migraine, non-oral formulations may be useful in a number of situations, including: acute migraine attacks requiring very rapid onset of efficacy; presence of nausea, vomiting, and/or dysphagia; or when oral medications have previously failed. Zavegepant nasal spray is a third-generation, high-affinity, selective, and structurally unique small molecule calcitonin gene-related peptide receptor (CGRP) antagonist. It is the only intranasal CGRP antagonist in late-stage development for the acute treatment of migraine, as Prof. Richard Bertz (University of Pittsburgh, PA, USA) explained.

At the AAN 2022 meeting, results were shared of 2 single-centre, phase 1, placebo-controlled, randomised, double-blind, sequential zavegepant studies [1]. Participants were non-smokers aged 18–55 years. In the single-dose study, 9 cohorts of 8 adults each received 0.1, 0.3, 1, 3, 5, 10, 20, or 40 mg intranasal zavegepant or placebo. In the multiple-dose study, 6 cohorts of 12 adults each received a daily dose of 5, 10, 20, or 40 mg or placebo for 8 or 14 days depending on the cohort.

Intranasal zavegepant was rapidly absorbed, with a median T_{max} ranging from 0.54 to 0.96 hours across doses. The increase in exposure was slightly less than dose-proportional at doses of 1 to 40 mg. Single doses of ≥10 mg produced an average C_{max} associated with ≥90% inhibition of CGRP signalling receptors, suggestive of efficacy in migraine.

Single and multiple daily doses of intranasal zavegepant were well tolerated. A maximum tolerated dose was not identified. The most common adverse events were associated with nasal administration and of mild intensity. No serious adverse events were detected, and no participants had levels of aminotransferases >3x or total bilirubin >2x the upper limit of normal. Effective half-life ranged from 5.0 to 7.6 hours,

with little accumulation after multiple daily doses.

1. Bertz R, et al. Safety, Tolerability, and pharmacokinetics of single and multiple ascending doses of intranasal zavegepant in healthy adults. S31.004, AAN 2022, 02–07 April, Seattle, USA.

Telemedicine during COVID-19 pandemic highly appreciated

On behalf of the American Migraine Foundation (AMF), the patient experience of telemedicine for headache care during the COVID-19 pandemic was evaluated. Telemedicine resulted in high patient satisfaction rates. Almost all participants indicated that they would prefer to continue to use telemedicine for their headache care.

Dr Chia-Chun Chiang (Mayo Clinic, MN, USA) presented the results of one of the first studies to assess the patient perspective of telemedicine for headache care [1]. The AMF designed a standardised electronic questionnaire with 15 questions that was sent to over 100,000 AMF members to evaluate the period between March and September 2020. The results were published in *Headache* in May 2021 [2].

Included were 1,172 respondents. The average age was 49.5 years; 1,017 (88%) were women. Of 1,127 respondents, 648 (57.5%) said they had used telemedicine visits for headache care during the study period. Among this group, 553 patients (85.5%) used it for follow-up visits; 94 (14.5%) for new patient visits. Of 633 patients, only 47 (7.4%) received a new diagnosis of a headache disorder from telemedicine evaluation, the others did not have a change in their diagnoses. A new treatment was prescribed to 358 out of 636 patients (52.4%).

Of 638 participants, the experience using telemedicine for headache care was rated as very good by 396 (62.1%), good by 132 (20.7%), fair by 67 (10.5%), poor by 23 (3.6%), and other by 20 (3.1%). Most patients (89.8%) said they would continue to use telemedicine for their headache care and treatment, though half of them (45%) not for all visits. Among 524 respondents who did not use telemedicine visits, 293 (56%) said there was no need, but 255 (48.7%) said they were unaware that it was an option.

The study also revealed several barriers of care through telemedicine, including costs and availability. Dr Chiang said these challenges could be addressed by expanding insurance coverage to reimburse telemedicine, even after the pandemic, to widely promote and broadcast the use of telemedicine, and to consider internet access as a necessity and to expand internet service broadly in society.

1. Chiang C-C, et al. Patient Experience of Telemedicine for Headache Care During the COVID-19 Pandemic: An American Migraine Foundation Survey Study. S4.010, AAN 2022, 02–07 April, Seattle, USA.
2. Chiang C-C, et al. Headache. 2021;61(5):734-739.

Multiple Sclerosis

Ublituximab versus teriflunomide in relapsing MS patients

In both the phase 3 ULTIMATE I and ULTIMATE II trial, ublituximab treatment demonstrated a statistically significant reduction in annualised relapse rate (ARR) and cumulative probability of first relapse compared with teriflunomide over 96 weeks in patients with relapsing multiple sclerosis (RMS).

Ublituximab is an investigational monoclonal antibody that targets a unique epitope on the CD20 antigen [1]. Binding to B cells, ublituximab triggers a series of immunological reactions, including antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). It is glyco-engineered to enhance ADCC [2].

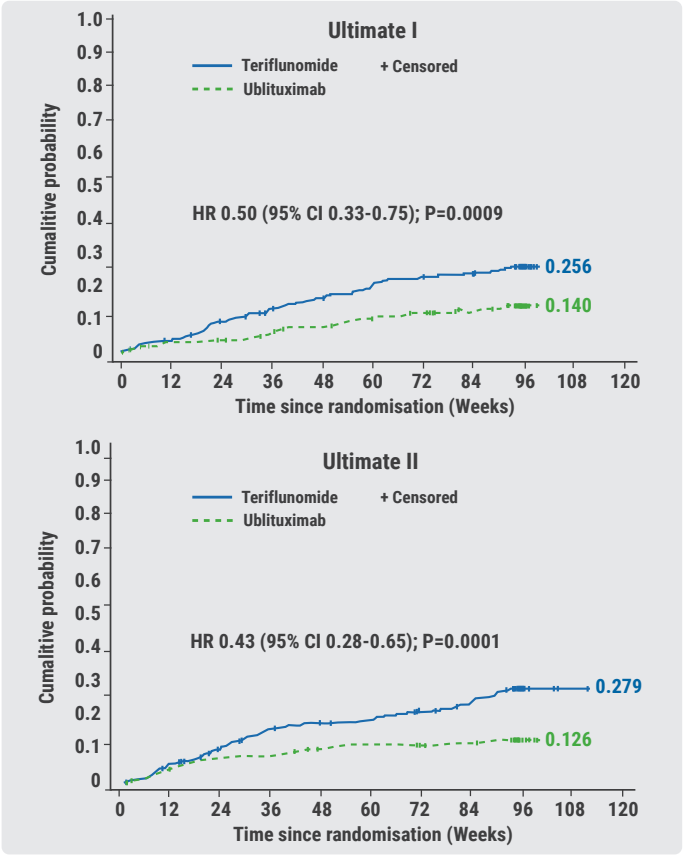
ULTIMATE I (NCT03277261) (n=549) and ULTIMATE II (NCT03277248) (n=545) are 2 independent phase 3, randomised, double-blind, active-controlled, global studies that evaluate the efficacy and safety/tolerability of ublituximab (450 mg intravenous infusion every 24 weeks, following a Day 1 infusion of 150 mg) versus teriflunomide (14 mg orally once daily) for 96 weeks. Participants were patients with RMS from 10 countries and most had relapsing-remitting MS, while about 2% had active secondary-progressive MS. In both studies, ublituximab previously showed significant relative improvements in

absolute risk reduction and radiographic disease activity [3]. Pre-specified analyses looked at the proportion of participants who were relapse-free and the time to first relapse. Prof. Lawrence Steinman (Stanford University, CA, USA) presented the results [4].

In the ULTIMATE I study, 86.7% versus 75.2% of participants were free of relapse with ublituximab and teriflunomide, respectively, after 96 weeks. In the ULTIMATE II study, these percentages were 87.5% and 73.5%, respectively. The estimated proportion of participants who remained relapse-free was higher with ublituximab than with teriflunomide in both studies.

The cumulative probability of first confirmed relapse was significantly lower with ublituximab in both studies than with teriflunomide. In ULTIMATE I the HR was 0.50 (95% CI 0.33–0.75; P=0.0007); in ULTIMATE II, the HR was 0.43 (95% CI 0.28–0.65; P<0.0001; see Figure).

Figure: Time to first confirmed relapse in ULTIMATE I and ULTIMATE II [3]



1. Babiker HM, et al. Expert Opin Investig Drugs. 2018;27(4):407–412.
2. Butler LA, et al. Blood Reviews. 2017;31(5):318–327.
3. Steinman L, et al. Abstract A-21–0076, EAN 2021, 19–22 June.
4. Steinman L, et al. Relapse Rate and Time to First Relapse Were Improved With Ublituximab vs Teriflunomide in the Phase 3 ULTIMATE I and ULTIMATE II Studies in Patients With Relapsing Multiple Sclerosis (RMS). Clinical Trials plenary session, AAN 2022, 02–07 April, Seattle, USA.

Ketogenic diet may improve disability and quality of life

A new study has found that a ketogenic diet is safe and tolerable over 6 months in patients with relapsing multiple sclerosis (MS) and has potential benefits. In a study with 65 participants, a ketogenic diet yielded improvements in body composition, fatigue, depression, quality of life, and neurological disability.

High-fat, low-carbohydrate ketogenic diets mimic a fasting state and have previously been shown to affect immune regulation, as explained by Dr J. Nicholas Brenton (University of Virginia Medical Center, VA, USA) [1]. To investigate the possible therapeutic potential of ketogenic diets, an open-label, uncontrolled study was set up that included 65 MS patients. They followed a ketogenic diet for 6 months and adherence was monitored on a daily basis by urine ketone testing. Patient-reported fatigue, depression, and quality-of-life scores were measured at baseline, as well as MS-related clinical outcome metrics. Baseline study metrics were repeated at 3 and 6 months while on a ketogenic diet.

Adherence to the ketogenic diet during the full study period was 83%. A ketogenic diet was associated with reductions in fat mass after 6 months compared with baseline (32.0 vs 41.3 kg; P<0.001) and a significant decline in fatigue and depression scores. MS quality-of-life physical (67 vs 79; P<0.001) and mental (71 vs 82; P<0.001) composite scores also improved. Additionally, Expanded Disability Status Scale scores (2.3 vs 1.9; P<0.001), 6-minute walk (1,631 vs 1,733 feet; P<0.001), and 9-hole peg test (21.5 vs 20.3 seconds; P<0.001) also improved following ketogenic diet. Dr Brenton concluded: "Our data justifies the need for future studies of ketogenic diets as a complementary therapeutic approach for the treatment of MS."

Another important (observational) study of the effect of diet in MS demonstrated a significant association between Mediterranean diet score and MS-related disability and brain atrophy [2]. The authors suggested the possibility of a neuroprotective mechanism, based on the observed strength of the relationship in progressive disease and partial mediation by third ventricle width. These results pave the way for interventional clinical trials.

1. Brenton JN, et al. Ketogenic diet as a strategy for improved wellness and reduced disability in relapsing multiple sclerosis. S40.007, AAN 2022, 02–07 April, Seattle, USA.
2. Katz Sand I, et al. Mediterranean diet score is associated with disability and brain atrophy in multiple sclerosis. S14.002, AAN 2022, 02–07 April, Seattle, USA.

Favourable additional safety data for ofatumumab

After up to 4 years of treatment, ofatumumab was still well tolerated in patients with relapsing multiple sclerosis (RMS); no new safety issues were identified. This was concluded from updated results of the ongoing, open-label, umbrella extension ALITHIOS trial.

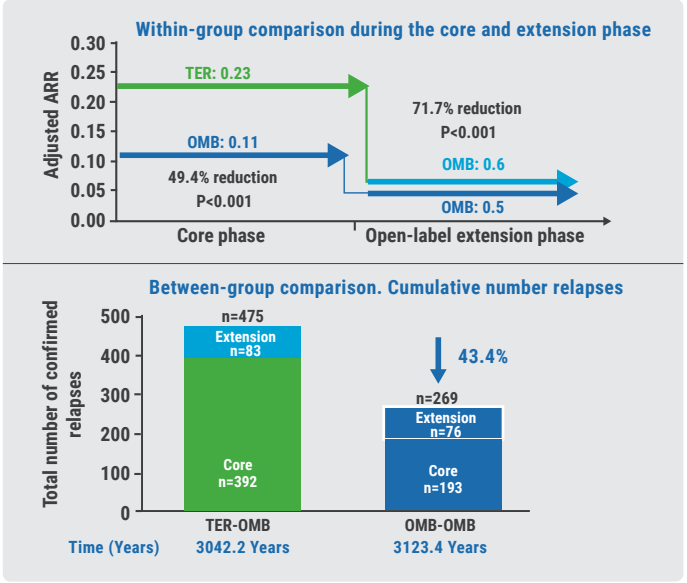
Ofatumumab is a fully-human, anti-CD20 monoclonal antibody developed for the treatment of adult RMS patients; the 20 mg dose is self-administered subcutaneously once a month [1]. Ofatumumab treatment up to 30 months was previously shown to have a favourable safety profile and to be generally well tolerated [2].

Cumulative data for up to 4 years of ofatumumab treatment were presented by Prof. Stephen Hauser (University of California, CA, USA) [3,4]. Patients had completed the core ASCLEPIOS I/II (NCT02792218, NCT02792231), APOLITOS (NCT03249714), or APLIOS (NCT03560739) clinical trial, after which they could continue ofatumumab treatment by entering the ALITHIOS trial (NCT03650114), regardless of treatment received in the core trial. At data cut-off, the overall study population counted 1,969 patients. Of these, 1,292 had received ofatumumab from the start, while 677 switched from teriflunomide to ofatumumab in the extension.

Adverse events (AEs) were registered in percentages and as exposure-adjusted incidence rate (EAIR). The results showed that 83.8% of patients had ≥1 AEs (EAIR 148.7) and 9.7% had ≥1 serious AEs (EAIR 4.8). Low incidence of serious infections (2.9%; EAIR 1.4) and malignancies (0.6%; EAIR 0.3) were detected. No association was found between IgG/IgM antibody levels and the risk of a serious infection: Levels of IgG were stable, while IgM decreased, but remained within normal ranges. Prof. Hauser concluded: "This additional safety data helps to confirm ofatumumab's longer-term safety profile and provides further confidence to the MS community."

Prof. Hauser also presented long-term efficacy data of ofatumumab in 1,214 patients [5]. Annualised relapse rate (ARR) remained low. Comparing both groups revealed 43.4% less relapses over 4 years in the group that had used ofatumumab from the start (see Figure). In this group there was also a reduced risk of 3-month (21.1%) and 6-month (19.6%) confirmed disability worsening and less disease activity, compared with the group that switched therapies.

Figure: Within-group and between-group comparisons of long-term ofatumumab efficacy [1]



AAR, annualised relapse rate; TER, teriflunomide; OMB, ofatumumab; TER-OMB, switch from teriflunomide to ofatumumab; OMB-OMB, continuous ofatumumab.

1. Kang C & Blair HA. Drugs. 2022;82(1):55–62.
2. Hauser SL, et al. N Engl J Med. 2020;383(6):546–557.
3. Hauser SL, et al. Long-term safety of ofatumumab in patients with relapsing multiple sclerosis. S14.004, AAN 2022, 02–07 April, Seattle, USA.
4. Hauser SL, et al. Mult Scler. Mar 1, 2022. DOI: 10.1177/13524585221079731.
5. Hauser SL, et al. Long-term efficacy of ofatumumab in patients with relapsing multiple sclerosis. P5.004, AAN 2022, 02–07 April, Seattle, USA.

Predicting new T2 lesions using a machine learning algorithm

A machine learning algorithm was able to detect abnormalities within normal-appearing white matter (NAWM) before any lesion could be detected. Using cross-sectional T1- and T2-weighted non-contrast brain MRI data from NAWM, this machine learning method could predict new T2 lesions up to 48 weeks prior to actual emergence.

Conventional MRI is not sufficiently sensitive to enable early diagnosis, nor is its specificity sufficient to predict disease severity. Machine learning analyses of brain scan data may help to fill this gap. Mr Bastien Caba (Biogen Digital Health, MA, USA) and colleagues analysed brain T1- and T2-weighted MRI scans from the pivotal, phase 3 ADVANCE trial (NCT00906399), which included 1,512 patients with relapsing-remitting multiple sclerosis (RRMS), to validate the algorithm [1]. They then tested this algorithm utilising MRIs of 886 patients with secondary progressive MS (SPMS) who participated in the ASCEND trial (NCT01416181).

Cubic patches with a 15 mm edge were sampled from NAWM of baseline scans. Patches co-locating with a future lesion at

48 weeks post-baseline were labelled positive; patches not associated with a future lesion in spatially matched white matter were negative. Texture-based radiomic features were extracted from the core and periphery of each patch, yielding 372 features per patch.

Of 40 selected features, 22 were core-based and 18 periphery-based; 18 were T1-based, 22 were T2-based. Applied on the ADVANCE validation set, the machine learning algorithm reached 66.4% balanced accuracy, 66.5% precision, 66.0% sensitivity, 66.8% specificity, and an area under the curve (AUC) of 72.6%. In the ASCEND cohort these percentages were 64.6%, 63.7%, 68.0%, 61.2%, and 71.4%, respectively.

"These results further inform our understanding of the nature of lesion formation in multiple sclerosis, which seemingly arises from areas of normal-appearing white matter that are in fact abnormal," concluded Mr Caba.

1. Caba B, et al. Machine learning-based prediction of new multiple sclerosis lesion formation using radiomic features from pre-lesion normal appearing white matter. S26.009, AAN 2022, 02–07 April, Seattle, USA.

Evobrutinib reduces volume of slowly expanding lesions

The highly selective Bruton's tyrosine kinase (BTK) inhibitor evobrutinib reduced the volume of slowly expanding lesions (SEL) in a phase 2 trial. This effect was dose-dependent and especially apparent in more advanced multiple sclerosis (MS). This is the first evidence that a BTK inhibitor impacts brain lesions associated with chronic inflammation and tissue loss.

Evobrutinib is a highly selective BTK inhibitor that targets B cells, macrophages, and microglia. In a phase 2 trial (NCT02975349) in patients with relapsing MS, 75 mg twice-daily evobrutinib reduced T1 gadolinium-enhancing lesions versus placebo during weeks 12 through 24 [1].

The current study focused on the effect of evobrutinib versus a comparator on an emerging MRI biomarker: SELs, also referred to as "smouldering lesions" [2]. SELs are chronically active, demyelinated MS lesions, likely driven by sustained microglia/macrophage activity. They can be detected in vivo as of the past few years. In this study, SELs were defined as radially expanding areas of pre-existing T2 lesions of ≥10 contiguous voxels, around 30 mm^3 in size. Evobrutinib at doses of 25 mg once daily (n=50), 75 mg once daily (n=51), and 75 mg twice daily (n=53) was compared with placebo/evobrutinib 25 mg once daily (n=53). SEL volume was analysed after 48 weeks or after end of treatment in RMS patients, both among those who completed or discontinued the study. Prof. Douglas Arnold (McGill University, Canada) shared the results.

Evobrutinib was found to decrease SEL volume relative to the comparator in a dose-dependent manner:

- 25 mg once daily, -136.5 mm^3 (P=0.505);
- 75 mg once daily, -246.0 mm^3 (P=0.192);
- 75 mg twice daily, -474.5 mm^3 (P=0.047).

In pooled, high-dose groups (75 mg once daily and 75 mg twice daily), SEL volume was significantly reduced compared with low-dose groups (placebo and evobrutinib 25 mg once daily) in the following subgroups:

- baseline EDSS ≥3.5: -652.0 mm^3 (P=0.020);
- relapsing-remitting MS: -317.0 mm^3 (P=0.025);
- disease duration ≥8.5 years; -729.3 mm^3 (P=0.040).

This is the first evidence that a BTK inhibitor impacts brain lesions associated with chronic inflammation and tissue loss, probably via microglia.

1. Montalban X, et al. N Engl J Med. 2019;380(25):2406–17.
2. Arnold D, et al. Effects of Evobrutinib, a Bruton's Tyrosine Kinase Inhibitor, on Slowly Expanding Lesions: An Emerging Imaging Marker of Chronic Tissue Loss in Multiple Sclerosis. S14.009, AAN 2022, 02–07 April, Seattle, USA.

Sustained long-term efficacy and safety of satralizumab in NMOSD

The favourable efficacy and safety profile of satralizumab was sustained with long-term treatment of neuromyelitis optica spectrum disorder (NMOSD) in the open-label extensions (OLE) of the controlled SAkuraSky and SAkuraStar trials. High proportions of AQP4-IgG+ patients remained free from relapse and worsening disability after 3.7 years. Safety was also sustained over a median exposure of 4 years.

Two separate presentations assessed the long-term efficacy and safety, respectively, of satralizumab in patients with aquaporin-4-IgG-seropositive (AQP4-IgG+) NMOSD. Prof. Jeffrey Bennett (University of Colorado Hospital, CO, USA) presented the efficacy results [1]. He explained that participants from the SAkuraySky (NCT02028884) and SAkuraStar (NCT02073279) trials could enter the OLE, in which they were all treated with satralizumab 120 mg. In SAkuraSky, participants had received satralizumab + baseline immunosuppressants; in SAkuraStar, satralizumab monotherapy.

Overall, 111 AQP4-IgG+ patients were evaluated, 49 from SAkuraSky and 62 from SAkuraStar. These analyses assessed the annualised investigator-reported protocol-defined relapse (iPDR) rate (ARR), as well as the proportion of patients who remained free from iPDR, severe iPDR, and sustained Expanded Disability Status Scale (EDSS) score worsening. Severe iPDR was defined as a ≥2 point increase in the EDSS score; sustained EDSS worsening was an EDSS increase of ≥2, ≥1, or ≥0.5 points for patients with baseline scores of 0, 1–5, or ≥5.5, respectively.

Efficacy of satralizumab was sustained in the long term, with high proportions of AQP4-IgG+ patients free from iPDR (71% in SAkuraSky and 73% in SAkuraStar) and free from severe iPDR (91% and 90%, respectively) at week 192 (3.7 years). Percentages of patients free from sustained EDSS worsening were 90% and 86%, respectively. ARR remained consistently low in satralizumab-treated patients. The overall adjusted ARR was low at week 192: in SAkuraSky, it was 0.12 (95% CI 0.08–0.18); in SAkuraSky, 0.08 (95% CI 0.05 to -0.13). The yearly ARR was never above 0.20, with a range of 0.02–0.20. Prof. Bennett mentioned that satralizumab will also be tested as a treatment of myasthenia gravis.

The long-term safety outcomes of satralizumab in the OLE of the SAkura studies were presented by Prof. Benjamin Greenberg (UT Southwestern Medical Center, TX, USA) [2]. The OLE included 75 participants of the SAkuraSky and 91 of the SAkuraStar trial. Median treatment exposure in the overall treatment period (DBP + OLE) was 4 years. Rates of (serious) adverse events, including (serious) infection, in the overall treatment period were comparable to those in the double-blind periods of both studies. No deaths or anaphylactic reactions related to satralizumab treatement were reported.

1. Kleiter I, et al. Long-term Efficacy of Satralizumab in Aquaporin-4-IgG-seropositive Neuromyelitis Optica Spectrum Disorder (NMOSD): Results from the Open-label Extension Periods of SAkuraSky and SAkuraStar. S25.009, AAN 2022, 02–07 April, Seattle, USA.
2. Greenberg B, et al. Long-term Safety of Satralizumab in Neuromyelitis Optica Spectrum Disorder (NMOSD): Results from the Phase 3 SAkuraSky and SAkuraStar Studies. S25.010, AAN 2022, 02–07 April, Seattle, USA.

Muscle and Neuro-Muscular Disorders

Ravulizumab in patients with generalised myasthenia gravis

In the randomised, phase 3 CHAMPION MG trial, the terminal complement component 5 (C5) inhibitor ravulizumab provided rapid and sustained symptomatic improvements in patients with generalised myasthenia gravis (MG) for up to 26 weeks. These effects were sustained after 26 weeks of open-label treatment.

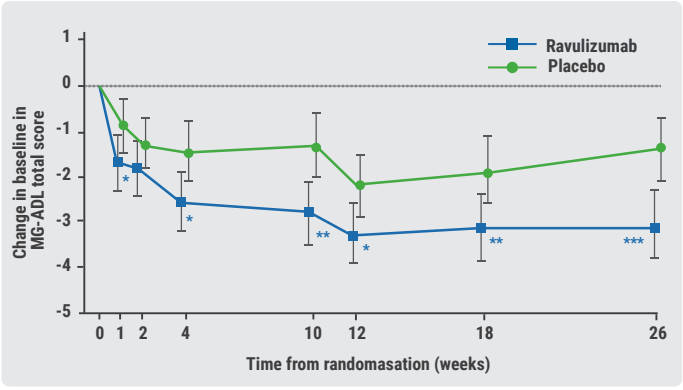
In most (~85%) generalised MG patients, binding auto-antibodies to the post-synaptic acetylcholine receptor (AChR) leads to activation of the complement cascade and generation of the membrane attack complex (MAC), resulting in the destruction of the post-synaptic membrane of the neuromuscular junction [1]. Treatment with a complement inhibitor led to significant improvements of symptoms in patients with refractory generalised MG [2].

The phase 3 CHAMPION MG trial (NCT03920293) enrolled 175 patients with AChR antibody-positive (AChR Ab+) generalised MG 1:1 to receive ravulizumab infusion or placebo for 26 weeks in 85 centres worldwide [3]. The experimental group received body weight-based doses of 2,400 to 3,000 mg induction on day 1, and 3,000 to 3,600 mg maintenance dose every 8 weeks starting on day 15. All participants were allowed background treatment with an acetylcholinesterase (AChE) inhibitor and an immunosuppressant. The primary efficacy endpoint was an improvement in Myasthenia Gravis Activities of Daily Living (MG-ADL). A secondary endpoint was Quantitative Myasthenia Gravis (QMG) total score. Dr Tuan Hoang Vu (University of South Florida Physicians Group, FL, USA) presented the results.

Ravulizumab was associated with a statistically significant improvement in MG-ADL total score versus placebo (-3.1 vs -1.4; P=0.0009; see Figure on the next page). QMG total score also improved significantly compared with placebo (P<0.001), as did the proportion of patients who achieved an improvement of at least 5 points in QMG (P=0.005). Improvements in MG-ADL and QMG scores had a quick onset, within 1 week, and were maintained through week 26. No significant improvements in quality of life were detected

at week 26, as measured by the Revised 15-Component Myasthenia Gravis Quality of Life score (P=0.064) or the Neuro-QOL Fatigue score (P=0.373). This result could have been influenced by the COVID-19 pandemic.

Figure: MG-ADL score improvements from week 1 through 26 [3]



*P<0.05; **P<0.01; ***P<0.001; MG-ADL, Myasthenia Gravis Activities of Daily Living; SEM, standard error of the mean.

Adverse events (AEs) were similar in both groups. The most frequently reported AEs in the ravulizumab and placebo group were headache (18.6% and 25.8%, respectively), diarrhoea (15.1% and 12.4%), and nausea (10.5% and 10.1%). Among serious AEs, the most frequent included MG crisis (ravulizumab: 1.2%) and MG worsening (placebo: 3.4%).

After completing the randomised-controlled period, participants could enter an open-label extension (OLE), during which they received ravulizumab for an additional 26 weeks [4]. After 52 weeks, treatment effects were sustained. Patients who had originally been assigned a placebo showed immediate and sustained improvements in MG-ADL and QMG scores in the OLE, which were comparable to those in the ravulizumab group during the randomised-controlled period.

1. Howard JF. Ann N Y Acad Sci. 2018;1412(1):113–128.
2. Howard JF, et al. Lancet Neurol. 2017;16(12):976–86.
3. Vu TH, et al. Efficacy and safety of ravulizumab in anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: phase 3 CHAMPION MG study. Clinical Trials Plenary Session, AAN 2022, 02–07 April, Seattle, USA.
4. Howard JF, et al. Long-term Efficacy and Safety of Ravulizumab, a Long-acting Terminal Complement Inhibitor, in Adults with Anti-Acetylcholine Receptor Antibody-Positive Generalized Myasthenia Gravis: Results from the Phase 3 CHAMPION MG Open-label Extension. S25.005, AAN 2022, 02–07 April, Seattle, USA.

Gene therapy effective in older patients with spinal muscular atrophy

The observational RESTORE study demonstrated efficacy of onasemnogene abeparvovec (OA) in patients with spinal muscular atrophy (SMA) aged 6 months or older at the time they received this gene therapy. Interventional trials of OA had already demonstrated safety and efficacy of OA in patients <6 months of age.

RESTORE (NCT04174157) is a comprehensive, prospective, multicentre, observational registry of patients with genetically-confirmed SMA across several countries. At the time of OA infusion, 117 patients were 6 months or older. Of these, 51 were 6–12 months old, 57 were 12–24 months, and 9 were 24 months or older. Most participants (n=73) had 2 copies of the *SMN2* gene; one third (n=38) received OA monotherapy, while 26 combined OA with nusinersen, risdiplam, or both, and 53 patients switched from nusinersen to OA. Prof. Laurent Servais (MDUK Oxford Neuromuscular Centre, UK) presented the results [1].

At infusion, two thirds of patients (n=76/114) were diagnosed with SMA type 1; 7/114 did not yet have any symptoms. Despite their older age and higher weight (41/84 patients ≥8.5 kilogram), almost all showed improvements.

Motor skills were evaluated with the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), ranging from 0 to 64, with higher scores indicating better function; 28 children had at least ≥2 evaluable CHOP INTEND assessments. Of this group, 25 had maintained or increased their score. There were 18 patients with an improvement of at least 4 points; 11 of them were 6–12 months old and 7 were 12–24 months.

No new or unexpected adverse events (AEs) were detected. Of 116 patients, 71 had at least 1 treatment-emergent AE; 33 had at least 1 serious AE, of which 20 were deemed related to OA treatment.

1. Servais L, et al. Effectiveness and safety of onasemnogene abeparvovec in older patients with spinal muscular atrophy (SMA): Real-world outcomes from the RESTORE registry. S39.002, AAN 2022, 02–07 April, Seattle, USA.

Losmapimod for facioscapulohumeral muscular dystrophy

Losmapimod showed improvement on relevant clinical endpoints in the treatment of facioscapulohumeral muscular dystrophy (FSHD) in the ReDUX4 trial. Its favourable safety and tolerability results support continued development.

FSHD is caused by the misexpression of the double homeobox protein 4 (DUX4) transcription factor in skeletal muscle. This condition ultimately results in progressive motor disability. Currently, no treatment options are available for FSHD that

prevent or slow muscle weakness and wasting. Losmapimod is an orally active, selective, small molecule inhibitor of p38α/β that reduced DUX4. It has been evaluated in over 3,500 subjects in clinical trials across 10 other indications, with no safety signals. The efficacy and safety results of losmapimod from the phase 2 ReDUX4 trial were presented by Prof. Al-Rabi N. Tawil (University of Rochester, NY, USA) [1]. Enrolled were 80 FSHD participants aged 18–65 years (mean age 46 years) who were randomised 1:1 to losmapimod (15 mg twice daily) or matching placebo.

Losmapimod exhibited expected pharmacokinetic and target engagement in blood and muscle. No difference was observed in DUX4-driven gene expression in muscle biopsy, which was the study's primary endpoint (26.16 for losmapimod vs 25.68 for placebo; difference 0.43; 95% CI -1.04–1.89; P=0.56). At week 48, losmapimod did demonstrate significantly better muscle health. Muscle fat infiltration (MFI) was 0.03% versus 0.52% (difference -0.49; 95% CI -0.86 to -0.12; P=0.01). Significant improvements were also measured in Reachable Workspace (RWS) with weights, Patients' Global Impression of Change (PGIC), and dynamometry. There was a non-significant slowing of progression in Timed Up and Go (TUG) completion, and no differences in FSHD-TUG, motor function measurement (MFM), or FSHD-Health Index.

Losmapimod was well tolerated with no serious drug-related adverse events (AEs). Treatment-emergent AEs occurred in 29 (73%) and 23 (58%) patients in the experimental and placebo group, respectively. In both groups, most treatment-emergent AEs were mild or moderate and deemed unrelated to study drug. A phase 3 trial is in preparation.

1. Tawil R, et al. A Phase 2, Randomized, Double-Blind, Placebo-Controlled, 48-Week Study of the Efficacy and Safety of Losmapimod in Subjects with FSHD: ReDUX4. S23.007, AAN 2022, 02–07 April, Seattle, USA.

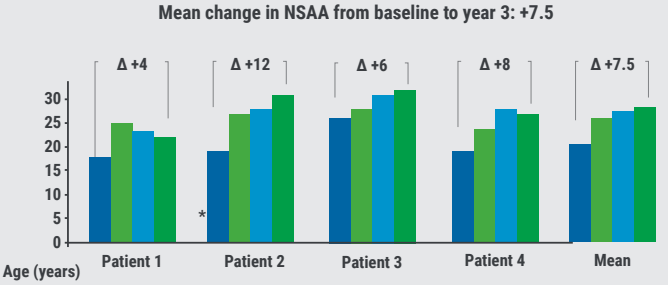
SRP-9001 for treating patients with Duchenne muscular dystrophy

The investigational gene therapy SRP-9001 (delandistrogene moxeparvovec) had a biological and possibly clinically relevant effect in children with Duchenne muscular dystrophy (DMD). The safety profile and durable response provides proof-of-concept support for continued clinical trials to assess SRP-9001 in patients with DMD.

SRP-9001 is developed for targeted expression of a shortened functional micro-dystrophin protein in skeletal and cardiac muscle. It uses the adeno-associated virus serotype rh74 (rAAVrh74) vector to deliver the micro-dystrophin-encoding gene to skeletal and cardiac muscle tissue. Efficacy and safety are evaluated in a three-part, phase 1/2 trial (NCT03769116) in patients with DMD. Participants were 4 ambulatory boys between 4 and 8 years old at study initiation with a confirmed *DMD* mutation between exons 18–58. They received a single intravenous infusion of SRP-9001 at an intended dose of $2.0x10^{14}$ vg/kg. The latest long-term (3-year; mean age of patients 8.2 years) safety and functional data from this study were presented by Dr Jerry Mendell (Nationwide Children's Hospital, OH, USA) [1].

North Star Ambulatory Assessment (NSAA) showed long-term overall improvements from baseline that were maintained over 3 years, indicating a durable response (see Figure). NSAA scores improved by a mean of 7.5 points overall. Dr Mendell stressed the importance of these outcomes. "There is no question about this treatment's unequivocal efficacy." One indication was the mean change from baseline in walking 100 metres, which improved by 10.3 seconds after 3 years. NSAA improvements were generally associated with improvement in ambulation over 3 years compared with decline generally expected in untreated natural history patients.

Figure: NSAA total scores over 3 years after SRP-9001 treatment [1]



Age (years)	Patient 1	Patient 2	Patient 3	Patient 4	Mean
At baseline	5.7	4.8	6.0	4.0	5.1
At year 1	6.8	5.8	7.1	5.1	6.2
At year 2	7.7	6.8	8.0	6.3	7.2
At year 3	8.7	7.8	9.1	7.1	8.2

No new safety signals were detected. Safety data were consistent with the wider SRP-9001 clinical trial program. Treatment-related safety events in this study mostly occurred in the first 90 days after infusion and all resolved. These results, said Dr Mendell, reinforce the overall long-term acceptable safety profile of SRP-9001.

1. Mendell JR, et al. A Phase 2 Clinical Trial Evaluating the Safety and Efficacy of SRP-9001 for Treating Patients with Duchenne Muscular Dystrophy. S23.002, AAN 2022, 2-7 April, Seattle, USA.

Cerebrovascular Disease and Stroke

Intravenous thrombolysis after ischaemic stroke: When in doubt, leave it out?

Results of the MR CLEAN-NO IV trial failed to show superiority (or non-inferiority) of direct endovascular treatment (EVT) compared with the combination of intravenous thrombolysis (IVT) and EVT. Does this imply guidelines need to be revised?

The publication of the original MR CLEAN trial established mechanical thrombectomy as a safe and effective treatment for acute ischaemic stroke caused by large-vessel occlusion [1]. IVT in eligible patients prior to EVT is still recommended, most notably in the guidelines of the European Stroke Organisation (ESO)–European Society for Minimally Invasive Neurological Therapy (ESMINT) [2]. This may however not be necessary. To bring more certainty, MR CLEAN-NO IV was carried out in 20 centres (16 in the Netherlands) capable of providing EVT. Dr Natalie LeCouffe (Amsterdam University Medical Centre, the Netherlands) presented the results [3,4].

The phase 3 MR CLEAN-NO IV study randomised 539 patients with acute ischaemic stroke to receive EVT alone (n=273) or EVT preceded by alteplase (n=266; standard of care). Median age was 71 years; 56.6% were men. Primary outcome was distribution on the modified Rankin Scale, on a scale of 0 (no complaints) to 6 (death). The results showed no significant difference, with an adjusted common odds ratio (acOR) of 0.84 (95% CI 0.62–1.14). "This difference was not statistically significant, nor was the combined treatment not inferior," Dr LeCouffe noted.

Recanalisation was successful after 24 hours in 83.1% of the combined treatment group and 78.7% of the EVT-only group (aOR 0.73; 95% CI 0.47–1.13), a non-significant difference. Functional outcomes did not differ between groups. Mortality rate was numerically higher in the EVT-only group, but again the difference was not significant (20.5% vs 15.8%; OR 1.39; 95% CI 0.84–2.30). No difference in risk of any intracranial haemorrhage (35.9% vs 36.4%; OR 0.99; 95% CI 0.70–1.41) or symptomatic intracranial haemorrhage (5.9% vs 5.3%; OR 1.31; 95% CI 0.61–2.84) was present. Dr LeCouffe said the latter finding was the most surprising one and contrary to what was expected.

Dr LeCouffe went on to present some preliminary results of a study-level meta-analysis on behalf of a new collaboration: Improving Reperfusion strategies in Ischemic Stroke (IRIS). Included were 6 similar trials: DIRECT MT, DEVT, DIRECT-SAFE, SKIP, SWIFT-DIRECT, and MR CLEAN-NO IV. The results showed a "suggestion of non-inferiority." There seems to be a trade-off between successful reperfusion and symptomatic intracranial haemorrhage. A patient-level meta-analysis is called for to identify subgroups (e.g. based on occlusion location) that might benefit or not from pre-treatment with IVT. Dr LeCouffe concluded that recommendations on adding IVT in recent stroke guidelines may have been premature and that the following maxim may apply instead: "When in doubt, leave it out."

1. Fransen PSS, et al. Trials. 2014;15:343.
2. Turc G, et al. J Neurointerv Surg. 2022;14(3):209.
3. LeCouffe N. MR CLEAN-NO IV: Intravenous treatment followed by endovascular treatment versus direct endovascular treatment for acute ischemic stroke caused by a proximal intracranial occlusion. Clinical Trials plenary session, AAN 2022, 02–07 April, Seattle, USA.
4. Treurniet KM, et al. Trials. 2021;22(1):141.

Better outcomes with mechanical thrombectomy in elderly stroke patients

Results of a meta-analysis suggest that a favourable outcome is more likely if mechanical thrombectomy is added to best medical management (BMM) in elderly patients with anterior circulation stroke due to large vessel occlusion (aLVO). Compared with BMM alone, adding mechanical thrombectomy did not increase mortality.

Mechanical thrombectomy is considered standard treatment for aLVO, but controversy still exists about the risk-benefit ratio and cost-effectiveness of performing this procedure in the elderly. Researchers therefore performed a systematic search to identify randomised trials up to October 2021 comparing treatment of aLVO patients with mechanical thrombectomy or BMM and reporting functional outcome. For this meta-analysis, patients were categorised as either elderly (>70 years) or non-elderly. Outcomes were evaluated based on the modified Rankin Scale score: a score ≤1 was considered excellent, ≤2 good, and ≥5 poor. Dr Aisha Ali (University of Illinois, IL, USA) presented the results [1].

The inclusion criteria were met by 6 trials: RESILIENT, DAWN, DEFUSE 3, ESCAPE, SWIFT PRIME, and REVASCAT. A total of 1,315 participants were included in the analysis, of whom 873 were non-elderly and 442 were elderly patients. In both age groups, mechanical thrombectomy yielded more favourable outcomes, especially in the non-elderly group. In the non-elderly group, the odds of all outcomes favoured mechanical thrombectomy over BMM:

- excellent outcome (OR 2.86; 95% CI 2.05–3.99; I2=0%);
- good outcome (OR 3.52; 95% CI 2.63–4.70; I2=0%);
- poor outcome (OR 0.5; 95% CI 0.36-0.70; I2=0%);
- mortality (OR 0.53; 95% CI 0.31-0.90; I2=0).

In the elderly group, the odds of all outcomes were also more favourable for mechanical thrombectomy, except for the excellent outcome and mortality:

- excellent outcome (OR 2.24; 0.93-5.38; I2=55%), no difference;
- good outcome (OR 2.11; 1.11-3.99; I2=46%);
- poor outcome (OR 0.5; 0.33-0.75; I2=6%);
- mortality (OR 0.6; 0.29-1.22; I2=34%), no difference.

So, even in elderly patients, it appears mechanical thrombectomy should be considered over BMM alone.

1. Ali A, et al. Efficacy and safety of mechanical thrombectomy in elderly patients. S17.008, AAN 2022, 02–07 April.

Plasma NfL levels associated with cardiovascular risk

Elevated levels of neurofilament light chain (NfL) are a known biomarker for neurodegeneration in conditions such as stroke, dementia, multiple sclerosis, and amyotrophic lateral sclerosis. A new study revealed that NfL may also be a risk marker for the onset of cardiac disease. Circulating NfL levels were found to be associated with future risk of all cardiovascular diseases, coronary heart disease, and heart failure, but only in minimally adjusted models.

To determine whether NfL is a risk marker for future cardiovascular disease, Dr Hugo Aparicio (Boston University School of Medicine, MA, USA) and colleagues determined plasma NfL levels of 2,048 participants in the community-based Framingham Heart Study Offspring and OMNI1 cohorts using a high-sensitivity, single-molecule array [1]. Mean age was 69 years, and 58% were women. All models were adjusted for age, sex, and cohort.

During the study period (2011–2019), 175 (8.5%) incident cardiovascular events were observed. With a mean 5.5 years of follow-up, baseline NfL levels were related to the incidence of cardiovascular disease and its individual components. Higher plasma NfL levels were associated with an increased risk of:

- coronary heart disease (n=67; HR 1.56; 95% CI 1.00–2.41);
- heart failure (n=91; HR 1.67; 95%CI 1.13–2.47);
- cardiovascular disease (HR 1.43; 95% CI 1.05-1.95)

However, no association was found between higher plasma NfL level and stroke (n=60; HR 1.00; 95% CI 0.56–1.78).

These associations were no longer significant after further adjusting the models for renal function, BMI, race, current smoking, diabetes, systolic blood pressure, anti-hypertensive treatment, and high-density lipoprotein level. The authors added that further research is needed to find out which of the adjusted risk factors attenuate the association between NfL and cardiac risk.

1. Aparicio H, et al. Association of Plasma NfL Levels with Risk of Cardiovascular Disease in the Framingham Heart Study. S33.005, AAN 2022, 02–07 April, Seattle, USA.

Non-invasive vagus nerve stimulation for acute stroke

In a first-in-human, sham-controlled study, non-invasive vagus nerve stimulation (VNS) was safe and feasible for the acute treatment of ischaemic and haemorrhagic stroke. Infarct growth was relatively small, which may be an indication of efficacy.

Results from preclinical studies have suggested that VNS can be helpful to treat acute stroke and facilitate the benefits of rehabilitation interventions. However, the invasive nature of this treatment clearly limits clinical application [1]. Non-invasive VNS is a recently developed alternative. Safety, feasibility, and potential efficacy of non-invasive VNS was assessed in a randomised, blind, sham-controlled, multicentre study. Prof. Ethem Murat Arsava (Hacettepe University, Turkey) presented the results [2].

A total of 68 participants admitted to 9 clinical sites had acute ischaemic (n=60) or haemorrhagic stroke (n=8) and all received standard care. They were randomised to receive low- or high-dose non-invasive VNS, or sham no later than 6 hours after onset of stroke. Non-invasive VNS was applied to 44 patients, sham to 24 patients. No differences were observed in baseline characteristics between the 2 groups. Low-dose non-invasive VNS consisted of 7 stimulations of 2 minutes each applied

to the skin overlying the vagus nerve every 10 minutes for 1 hour; high-dose non-invasive VNS was a double amount of 14 stimulations of 2 minutes every 10 minutes during hour 1 and hour 5. Safety was assessed 2 and 5 minutes after each stimulation and 30 minutes after the final stimulation, and included measures of severe bradycardia (≤50 beats/min) and significant hypotension (≥20 mmHg reduction in arterial blood pressure). Efficacy was evaluated in terms of absolute and relative infarct growth, measured by diffusion-weighted imaging, at baseline and 24 hours post stroke, and the percentage of patients with an NIH Stroke Scale (NIHSS) score of ≤4 points, or with a ≥8-point improvement after 24 hours.

The active treatment showed to be feasible, with all patient receiving all intended stimulation. The results further suggest that non-invasive VNS is safe, as it was not associated with a significantly higher risk of either bradycardia (non-invasive VNS 3.1% vs sham 2.9%; P=0.965) or hypotension (non-invasive VNS 2.5% vs sham 1.1%; P=0.145). No acute coronary syndrome, symptomatic intracerebral haemorrhage, or stimulation site reactions were detected, nor were there any deaths.

Clinical efficacy measures were similar in the sham and non-invasive VNS group. Relative infarct growth was considerably lower in the high-dose non-invasive VNS group than in the sham group (63.3% vs 185.8%; P=0.05), indicating possible efficacy.

1. Li L, et al. Front Neurosci. 2022;16:820665.
2. Arsava EM, et al. Non-invasive vagus nerve stimulation for the acute treatment of stroke. S17.010, AAN 2022, 02–07 April, Seattle, USA.

Parkinson's Disease

Prasinezumab in Parkinson's disease: delayed-start analysis of PASADENA trial

An efficacy signal of prasinezumab after 52 weeks in part 1 of the PASADENA study was further evaluated in an exploratory delayed-start analysis of part 2 of PASADENA. In patients with early Parkinson's disease (PD), the difference in MDS-UPDRS Part III in the early-start versus the delayed-start group persisted after 104 weeks.

Prasinezumab is a humanised, monoclonal antibody specifically designed to target α-synucleinopathy (α-Syn) in PD. Prasinezumab demonstrated efficacy in multiple *in vivo* and cellular α-Syn-models. It has the potential to slow PD progression by protecting neurons from toxic α-Syn species.

The effect of prasinezumab was evaluated in the placebo-controlled, phase 2 PASADENA study (NCT03100149). The primary endpoint was the Movement Disorders Society–Unified Parkinson's disease Rating Scale (MDS-UPDRS) sum of Parts I, II, and III at week 52. This endpoint was not met, but prasinezumab showed a favourable safety profile and a signal of reduction in clinical decline, as indicated by the MDS-UPDRS Part III bradykinesia score [1]. This persistent signal was further evaluated in early PD patients using a delayed-start analysis of part 2 (week 104) of the PASADENA study. Dr Gennaro Pagano (King's College London, UK) presented the results [2].

Participants with early PD (diagnosis ≤2 years at screening) were randomised to intravenous prasinezumab every 4 weeks (1,500 or 4,500 mg) for 104 weeks (early-start group; n=204), or placebo for 52 weeks followed by prasinezumab (1,500 or 4,500 mg) for 52 weeks (delayed-start group; n=105).

Worsening from baseline in MDS-UPDRS Part III scores was less in the early-start group than in the delayed-start group (5.02 vs 6.25 points at week 52; 9.18 vs 11.12 points at week 104). The largest group difference was in the bradykinesia subscore. In the early-start group, fewer patients reached a ≥5-point increase in MDS-UPDRS Part III: 79.1% versus 89.5% in the delayed-start group (HR 0.77; 80% CI 0.66–0.91). Further studies will have to confirm these findings. The ongoing, phase 2b PADOVA (NCT04777331) study will further assess efficacy and safety of prasinezumab in early PD patients on stable symptomatic treatment.

1. Pagano G, et al. Mov Disord. 2020;35(suppl 1).
2. Pagano G, et al. A 104-week delayed-start analysis of PASADENA (Phase II study evaluating the safety and efficacy of prasinezumab in early Parkinson's disease). S16.008, AAN 2022, 02–07 April, Seattle, USA.

IPX203 versus immediate release carbidopa-levodopa

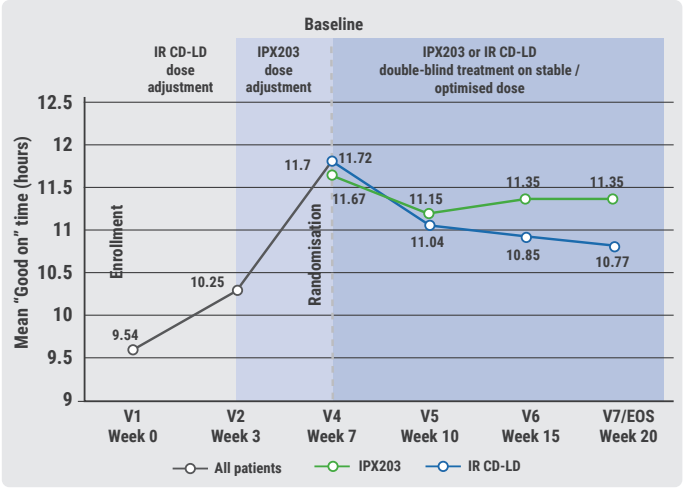
The RISE-PD study compared the safety and efficacy of IPX203 with immediate release carbidopa-levodopa (CD-LD) in Parkinson's disease (PD) patients with motor fluctuations. IPX203, an investigational oral extended-release (ER) formulation of CD-LD, resulted in statistically significant improvement in "good on" time versus immediate release CD-LD, while requiring fewer daily dosages.

IPX203 was specifically designed to provide rapid levodopa absorption to quickly reach the desired plasma concentration and to maintain levodopa concentrations within the therapeutic range for a longer period of time than immediate release CD-LD, and with less peak-to-trough fluctuation. Prof. Robert Hauser (USF Parkinson's Disease and Movement Disorders Center, FL, USA) explained that the phase 3 RISE-PD study (NCT03670953) was meant to test the efficacy and safety of IPX203 and enrolled 506 participants aged 40 years and older (mean age of 66 years) with PD and motor fluctuations, who had at least 2.5 hours daily "off" time (no adequate symptom control) on average during waking hours [1].

For the first 3 weeks, participants underwent dose-adjusting, open-label treatment with immediate release CD-LD, followed by 4 weeks of open-label IPX203 treatment. Participants then entered a double-blind maintenance phase of 13 weeks, where they received either IPX203 (n=256), dosed on average 3 times a day (never more frequently than every 6 hours), or standard immediate-release CD-LD (n=250), dosed on average 5 times a day. Dosing adjustments were allowed to achieve an optimal response. Efficacy was measured at week 20 and the primary endpoint was "good on" time in hours per day, defined as the sum of "on" time without dyskinesia and "on" time with non-troublesome dyskinesia.

The results showed both an improvement from baseline in terms of "good on" time and a corresponding reduction in "off" time (see Figure). IPX203 led to an average of 0.53 more hours of "good on" time per day versus immediate-release CD-LD (P=0.0194). Consistently, "off" time was reduced by 0.48 hours per day on average (P=0.0252). The Patient Global Impression of Change (PGI-C) score, based on clinician assessment, showed that 29.7% of participants treated with IPX203 had a much or very much improved general health, versus 18.8% of participants treated with immediate-release CD-LD (P=0.0015). Change from baseline in the assessment of disability (Movement Disorders Society–Unified Parkinson's disease Rating Scale [MDS-UPDRS] Part III scores) was similar in both treatment groups. Prof. Hauser stressed the "critical importance" of the observation that the significant differences in favour of IPX203 were apparent despite it being dosed on average only 3 times a day. The most common treatment-emergent adverse effects were nausea, falls, and urinary tract infections.

Figure: IPX203 demonstrated significant improvement "good on" time from baseline to end of study [1]



IR CD-LD, immediate release carbidopa-levodopa.

A poster reported the mean duration of "good on" time per dose for IPX203 versus immediate-release CD-LD, which was established in a post-hoc analysis [2]. IPX203 provided 1.55 more hours (3.76 vs 2.21 hours) of "good on" time per dose, representing a 70% increase.

1. Hauser RA, et al. A phase 3 trial of IPX203 vs CD-LD IR in Parkinson's Disease patients with motor fluctuations (RISE-PD). S16.010, AAN 2022, 02–07 April, Seattle, USA.
2. Hauser RA, et al. Duration of benefit per dose: Post hoc analysis of "good on" time per dose for IPX203 vs CD-LD IR in the RISE-PD Phase 3 trial. P10.002, AAN 2022, 02–07 April, Seattle, USA.

Impact of COVID-19 public health interventions

COVID-19 public health interventions were associated with worsening sleep habits and exercise frequency, as well as greater dependency in daily living among patients with Parkinson's disease (PD). No association could be found with worsening movement symptoms or increasing need for levodopa.

The effects of public health interventions in response to the COVID-19 pandemic on outcomes in PD patients are unknown. A study was conducted to determine the impact of those interventions on mood, movement, and quality of life of

PD patients [1]. More specifically, Mr Ari Vandersluis (Heritage College of Osteopathic Medicine, OH, USA) and colleagues focused on possible consequences of disrupting lifestyle behaviours known to favour PD outcomes (such as exercise and social interaction frequencies), as well as the introduction of telemedicine for outpatient visits.

Both before and after the onset of COVID-19 public health interventions, comprehensive clinical assessments were carried out in 150 PD patients. The first visit was in-person, the second visit by telephone call. Results of the second, post-COVID visit showed an increase in the Hoehn and Yahr scale, a scale to rate PD progression, compared with the first, pre-COVID visit (n=122; 2.02 vs 1.86; P=0.006) Several non-movement PD symptoms were found to have worsened during the subsequent visit, including activities of daily living status, exercise frequency, and sleep disturbance frequency. There was generally no worsening of movement symptoms, including bradykinesia, rigidity, resting tremor, gait abnormality, and falls. The need for levodopa did not increase.

1. Vandersluis A, et al. Evaluating Outcomes in Parkinson's Disease Patients Following COVID-19 Interventions. S16.007, AAN 2022, 02–07 April, Seattle, USA.

COVID-19

Cognitive, EEG, and MRI features in COVID-19 survivors

For the first time, long-term neurocognitive and neurophysiological consequences of COVID-19 have been assessed. Patients showed interrelated cognitive, EEG, and MRI alterations 2 months after hospital discharge. Cognitive and EEG findings improved at 10 months. Dysgeusia and hyposmia during acute COVID-19 were related to increased vulnerability of memory over time.

Cognitive impairment has been reported in 81% and 21% of patients at 3 and 6 months after SARS-CoV-2 infection, respectively [1,2]. Psychiatric disturbance is present in 56% after 1 month and in 25% after 6 months [3,4]. Proposed pathogenic contributors are direct cerebral viral invasion and cellular damage, systemic inflammation through cytokine release, and cerebral microvascular changes [5]. Neuropathological studies have shown pronounced microglia activation and microthrombosis within white matter, mainly in the brain stem. Concerns about long-lasting neurological consequences of COVID-19 are growing, but there is a lack of longitudinal studies with long-term follow-up and structured neuropsychological assessments, and there is a complete lack of EEG studies focused on the post-COVID-19 phase.

Dr Giordano Cecchetti (Vita-Salute San Raffaele University, Italy) and colleagues set up a study to explore cognitive, EEG, and MRI features in COVID-19 survivors up to 10 months after hospital discharge [6,7]. Patients (n=49) with a recent diagnosis of COVID-19 underwent neuropsychological assessments investigating the main cognitive domains (global cognition, executive functions, memory, visuospatial functions, language) and 19-channel EEG within 2 months after hospital discharge; 33 patients repeated this within 10 months. A brain MRI was additionally performed at baseline in 36 participants. Of the 49 participants, 42 (86%) were treated as inpatients and 13 (27%) required non-invasive mechanical ventilation (NIMV).

Two months after SARS-CoV-2 infection, 53% of patients had cognitive impairment (16% executive impairment, 6% memory impairment, 6% visual-spatial impairment, 25% multi-domain impairment) and 28% showed psychopathological disturbance (10% depression, 12% PTSD, 6% depression + PTSD). Executive dysfunction correlated with the severity of the acute-phase respiratory distress, which was measured using the National Early Warning Score (NEWS). After 10 months, the percentage of patients with cognitive impairment had decreased to 36% (3% executive impairment, 6% memory impairment, 6% visual-spatial impairment, 21% multi-domain impairment), whereas the percentage with psychiatric symptoms remained the same (6% depression, 18% PTSD, 9% depression + PTSD). Patients with dysgeusia/hyposmia during acute-phase COVID-19 showed a significantly slower recovery of cognition than those without. A lower EEG delta band at baseline predicted worse cognitive functioning at follow-up. MRI analysis revealed prominent cerebrovascular alterations in COVID-19 patients, correlating with worse memory function at baseline and with

the total number of cardiovascular risk factors. On the other hand, no relation with severity of acute COVID-19 was found. Whether the observed alterations were directly linked to the infection or rather to its consequences is yet to be determined, as well as their reversibility.

1. Mazza MG, et al. Brain Behav Immun. 2021;94:138-147.
2. Del Brutto OH, et al. Eur J Neurol. 2021;28(10):3245-3253.
3. Mazza MG, et al. Brain Behav Immun. 2020;89:594-600.
4. Huang C, et al. Lancet. 2021;397(10270):220-232.
5. Heneka MT, et al. Alzheimers Res Ther. 2020;12(1):69.
6. Cecchetti G, et al. Cognitive, EEG and MRI features of COVID-19 survivors: a 10-month study. Contemporary Clinical Issues, AAN 2022, 02–07 April, Seattle, USA.
7. Cecchetti G, et al. J Neurol. Mar 6, 2022. DOI: 10.1007/s00415-022-11047-5.

Neurological manifestations of COVID-19 worsen prognosis

Results of a large, prospective study of hospitalised adults with SARS-CoV-2 infection showed that encephalopathy at admission was common and associated with worse outcomes. Serious neurological manifestations including stroke, seizure, and meningitis/encephalitis, though less common, were all associated with increased ICU support utilisation, more severe disease, and worse outcomes.

Prospective, multicentre data on neurological manifestations of COVID-19 are still scarce. A prospective, observational study of hospitalised adults with laboratory-confirmed SARS-CoV-2 infection described the prevalence, associated risk factors, and outcomes of serious neurological manifestations, notably encephalopathy, stroke, seizure, and meningo-encephalitis. The database consisted of 16,225 hospitalised adults in 179 hospitals in 24 countries, enrolled in the SCCM Discovery VIRUS COVID-19 registry (NCT04323787), with available discharge data. Dr Anna Cervantes-Arslanian (Boston University School of Medicine, MA, USA) presented the results [1]. Results were also published in *Critical Care Explorations* in April 2022 [2].

Of the study population, 2,092 (12.9%) developed serious neurological manifestations: 1,656 (10.2%) presented with encephalopathy at admission, 331 (2.0%) had a stroke, 243 (1.5%) had a seizure, and 73 (0.5%) had meningitis/encephalitis at admission or during their stay in the hospital. Risk factors for serious neurological manifestations were older age and higher prevalence of chronic medical conditions, including vascular diseases. Patients with severe neurological manifestation were less likely to have systemic viral symptoms (fever, dyspnoea, and cough) and were less likely to have milder neurological symptoms such as headache, anosmia, and dysgeusia.

All of the serious neurological manifestations were associated with more severe disease, increased ICU support utilisation, and worse outcomes: In patients with serious neurological manifestations the OR for more serious disease, as defined by the WHO ordinal disease severity scale, was 1.82 (P<0.001). The OR for admittance to the ICU was 1.45 (P<0.001). ICU interventions were also more frequent: OR 1.78 for extracorporeal membrane oxygenation (P=0.009) and OR 1.99 for replacement therapy (P<0.001). Hospital and 28-day mortality were higher (OR 1.51 and 1.58; P<0.001), while the number of ICU-free, hospital-free, and ventilator-free days was lower (estimated difference in days -0.84, -1.34, and -0.84; P<0.001).

1. Cervantes-Arslanian AM, et al. Neurologic Manifestations of Patients Hospitalized with COVID-19 in the SCCM VIRUS Registry. S18.001, AAN 2022, 02–07 April, Seattle, USA.
2. Cervantes-Arslanian AM, et al. Crit Care Explor. 2022;4(4):e0686.

New evidence for biological basis of "COVID-19 brain fog"

Most patients with cognitive post-acute sequelae of SARS-CoV-2 infection (PASC) who had mild COVID-19 symptoms had elevated levels of CSF immune activation and immunovascular markers compared with controls. These findings confirm the hypothesis that the condition often referred to as "brain fog" has a neurological (as opposed to psychological) basis and is linked to immune dysfunction.

Initial findings of the presented study were published in early 2022, in which the authors reported a high rate (77%; 10/13) of cognitive PASC patients with a CSF abnormality on clinically available tests versus 0% (0/4) of cognitive controls [1]. To further clarify how to identify patients with cognitive PASC and its biological correlates, 23 patients were followed who presented with new, persistent, cognitive PASC while recovering from relatively mild SARS-CoV-2 infection not requiring hospitalisation [2]. Ten recovering patients without PASC served as a control group. All participants underwent neurological examination and neuropsychological testing; 54% (n=13 cognitive PASC, n=5 controls) also agreed to lumbar puncture enabling analysis of immune activation and immunovascular markers in CSF. Lumbar puncture was performed after a median of 10.2 months following initial COVID-19 symptoms. Dr Joanna Hellmuth (University of California, CA, USA) shared the results.

CSF of participants with cognitive PASC contained higher median levels of the acute-phase reactant C-reactive protein

(0.007 vs 0.000 mg/L; P=0.004) and of serum amyloid A (0.001 vs 0.000 mg/L; P=0.001) compared with controls. Furthermore, the PASC group had non-significantly higher levels of the CSF immune activation markers IFN-γ-inducible protein (IP-10; P=0.059) and IL-8 (P=0.059); and of the immunovascular markers vascular endothelial growth factor-C (VEGF-C, P=0.095) and VEGFR-1 (P=0.059).

Within the cognitive PASC group, early onset of "brain fog" was associated with higher levels of CSF VEGF-C compared with delayed-onset cognitive PASC, defined as ≥1 month after the first COVID-19 symptoms. In 7 participants with acute-onset cognitive PASC, mean VEGF-C in CSF was 173 pg/mL compared with 99 pg/mL in 5 participants with delayed-onset cognitive PASC (P=0.048) and compared with 79 pg/mL in controls (P=0.048). Compared with controls, participants with acute-onset cognitive PASC also had elevated levels of CSF IP-10 (P=0.030), IL-8 (P=0.048), placental growth factor (P=0.030), and intercellular adhesion molecule-1 (P=0.045). Overall, Dr Hellmuth concluded that acute cognitive changes may be linked to prolonged disruption of immune homeostasis. A limitation of the study was the small number of participants.

1. Apple AC, et al. Ann Clin Transl Neurol. 2022;9(2):221–6.
2. Oddi A, et al. Cognitive Symptoms After Mild SARS-CoV-2 Infection Associate with Higher Levels of CSF Immune Activation and Immunovascular Markers. Emerging Science, AAN 2022, 02–07 April, Seattle, USA.